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(71) Applicant: **Japan Tobacco Inc.**
4-12-62 Higashishinagawa
Shinagawa-ku, Tokyo 140(JP)
Applicant: **Hasegawa, Akira**
1735-160, Kano-Okurayama
Gifu-shi Gifu-ken(JP)

(72) Inventor: **HASEGAWA, Akira, 1735-160,**
Ohkurayama Kano
Gifu-shi
Gifu-ken 501-31(JP)
Inventor: **UESATO, Shinichi, Pharmaceutical Research Lab.**
of Japan Tobacco Inc., 6-2, Umegaoka,
Midori-ku,
Yokohama-shi, Kanagawa-ken 227(JP)
Inventor: **ISHIDA, Tomio, Pharmaceutical Research Lab.**
of Japan Tobacco Inc., 6-2, Umegaoka,
Midori-ku,
Yokohama-shi, Kanagawa-ken 227(JP)
Inventor: **SAITO, Yutaka, Pharmaceutical Research Lab.**
of Japan Tobacco Inc., 6-2, Umegaoka,
Midori-ku,
Yokohama-shi, Kanagawa-ken 227(JP)
Inventor: **KISO, Makoto, 57-47, Monju**
Motosucho
Motosu-gun
Gifu-ken 501-12(JP)

(74) Representative: **Reinhard, Skuhra, Weise**
Postfach 44 01 51 Friedrichstrasse 31
W-8000 München 40(DE)

(54) **4,6-O-HYDROXYPHOSPHORYLGLUCOSAMINE DERIVATIVE.**

(57) A 4,6-O-hydroxyphosphorylglucosamine derivative of general formula (I) and a pharmaceutically acceptable salt thereof, wherein R_1 and R_2 represent each hydrogen or hydroxyl; one of R_3 and R_4 represents $-OCO(CH_2)_nCH_3$, $-CH_2(CH_2)_nCH_3$ or $-O-CH_2(CH_2)_nCH_3$ and the other represents hydrogen; l represents an integer of 4 to 16; m represents an integer of 4 to 16; and n represents an integer of 6 to 18.

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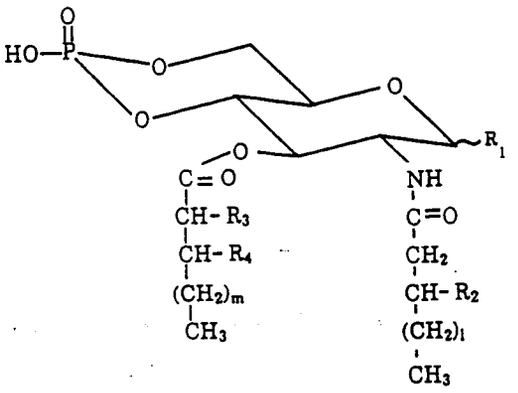


[1]

[Technical Field]

This invention relates to novel 4,6-O-hydroxyphosphoryl-glucosamine derivatives and pharmaceutically-acceptable salts thereof.

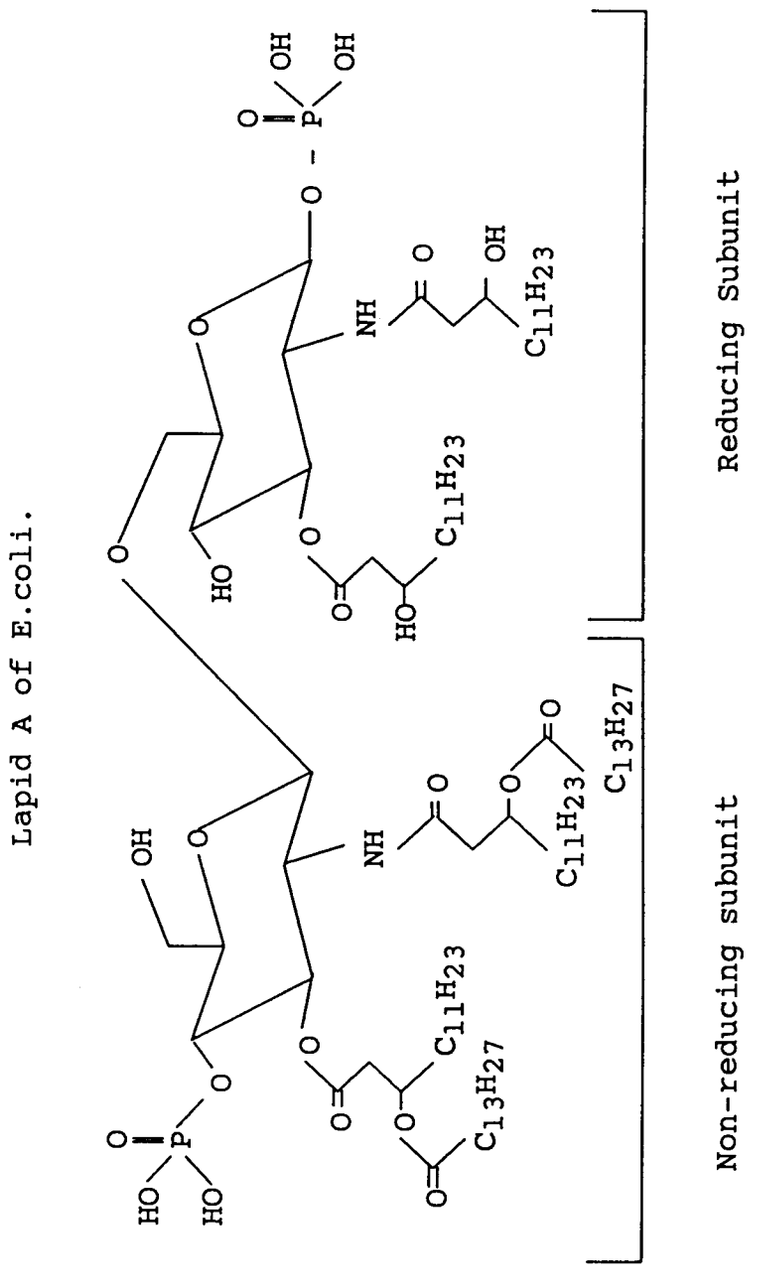
The compounds of the present invention show lipid A-like activity, and are useful as pharmaceutical drugs such as immunopotentiation agent and anti-tumour agent.

[Background Art]

Surface layers of Gram-negative bacteria are composed of a cell membranes, a cell wall peptidoglycan, and an outer membrane. The outer membrane contains lipopolysaccharides (hereinafter abbreviated LPS). LPS is a main ingredient of endotoxin which induces endotoxin shock, and consists of an acidic protein component, a high-molecular polysaccharide component, and a phospholipid component.

LPS induces various morbid conditions such as pyrogenesis, bleeding, arthritis, and encephalomyelitis. LPS is also known to show a host protection effect of immune-activating mechanism such as macrophage-activation, B-cell blastogenesis activity, and cell-mediated immunity-activation, as well as antitumour effect such as IFN(interferon) induction and TNF(tumour necrosis factor) induction.

A main part of LPS which shows these activities among said three parts is a phospholipid part, which is called lipid A. The lipid A comprises fatty acid residue and phosphoric acid both of which are combined with disaccharide amine, and has the following formula [Japanese Bacteriology Journal 40(1), 57(1985) and Proc.Natl.Acad.Sci.USA 80, 4624(1983)]:



A recent study has revealed that either a non-reducing subunit or a reducing subunit as shown above alone can show the lipid A-like activity, and various analogues have been synthesized based on this finding. Examples of the analogues are disclosed in European Patent Application Disclosure No.224260, Japanese Patent Application Disclosure No.62888/90, and Japanese Patent Application Disclosure No. 25494/90, etc..

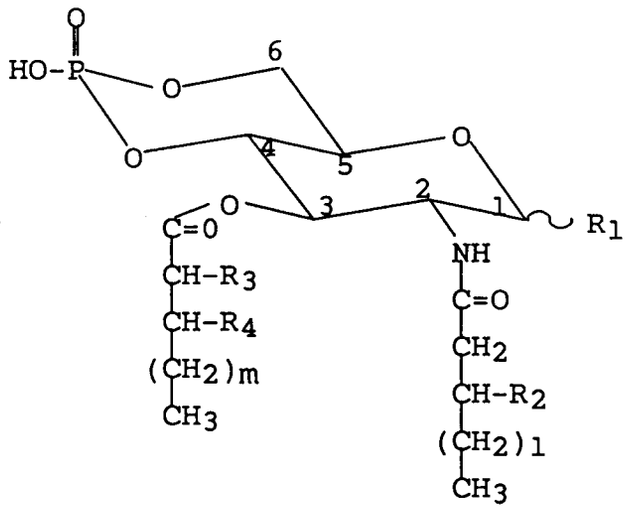
As described above, extensive studies have been conducted in order to obtain lipid A analogues, specifically by modifying them with various substituents and by changing substituent sites introduced. However, no lipid A analogue has been developed which can be pharmaceutically applicable, mainly because the same substituent shows the different activities depending on its introduced site, thus making the study on pharmaceutical application of the lipid A-like analogues difficult. Therefore, lipid A analogue of higher activity and lower toxicity is expected to develop.

[Disclosure of Invention]

The object of the invention is to produce novel compounds which show a more effective lipid A-like activity and low toxicity.

Inventors of the present invention have been energetically studied on lipid A derivatives in order to attain said object. As the result, the inventors have found novel compounds which show strong lipid A-like activity such as mytogenic activity of varying strengths depending on analogues, TNF-inducing activity, and IFN-inducing activity, and which nevertheless show low toxicity, and have completed the present invention based on this findings.

Novel 4,6-O-hydroxyphosphoryl-glucosamine derivatives according to the present invention have the following general formula [I]:



[I]

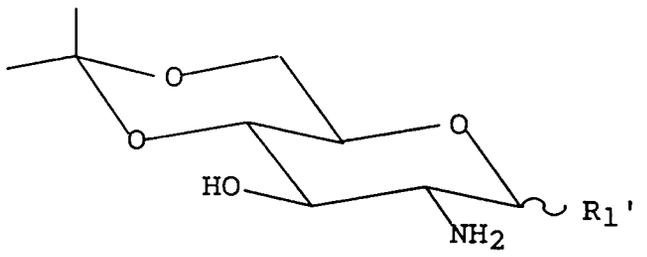
wherein R_1 and R_2 indicate a hydrogen atom or a hydroxy group; one of R_3 and R_4 is $-OCO(CH_2)_nCH_3$, $-CH_2(CH_2)_nCH_3$, or $-O-CH_2(CH_2)_nCH_3$ and the other is a hydrogen atom; l is an integer of 4-16; m is an integer of 4-16; and n is an integer of 6-18.

This invention also relates not only to said compounds but also to their pharmaceutically-acceptable salts. Examples of these salts are inorganic alkali metal salts, alkali-earth metal salts, and organic amine salts. Specifically, salts of the compounds with sodium, potassium, lithium, calcium, triethanolamine, diethanolamine, monoethanolamine, triethylamine, etc. are exemplified.

4,6-O-hydroxyphosphoryl-glucosamine derivatives [I] according to the present invention have two structural characteristics as follows. First, the pyranose ring is acylated at the 3-position with α- or β-alkylated fatty acids, α- or β-alkoxylated fatty acids, or α- or β-acyloxylated fatty acids. Second, hydroxyphosphoryl groups [>P(0)OH] are introduced to the 4- and 6-positions of the pyranose ring. The present compounds [I] are expected to be useful through these characteristics as pharmaceutical drug such as immune-activating agent. The present invention also includes all stereoisomers of the compounds [I] and a mixture thereof.

These compounds [I] can be produced according to the following reaction steps:

FLOW 1



R_1'=-H or -OSE

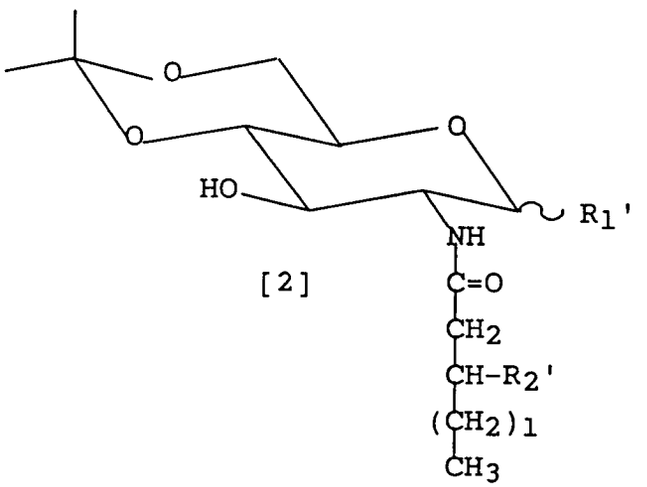
SE=$-CH_2CH_2Si(CH_3)_3$

[1]

FIRST STEP

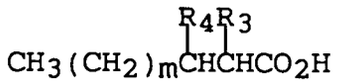
R_2'=-OSEM or -H

SEM=$-CH_2OCH_2CH_2Si(CH_3)_3$



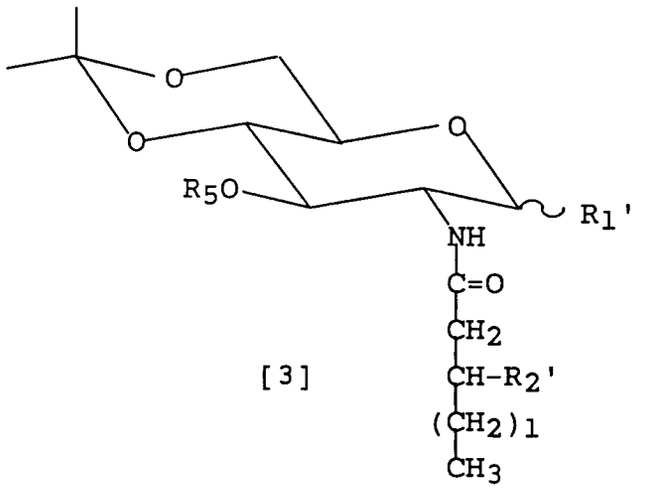
[2]

SECOND STEP

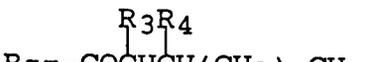


one of R_3, R_4 is $-OCO(CH_2)_nCH_3$, $-CH_2(CH_2)_nCH_3$ or $-OCH_2(CH_2)_nCH_3$;

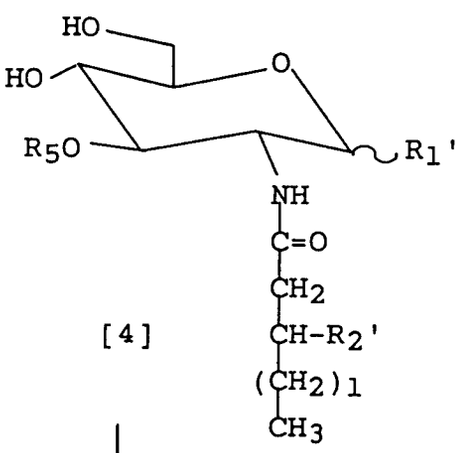
the other of them is Hydrogen



[3]

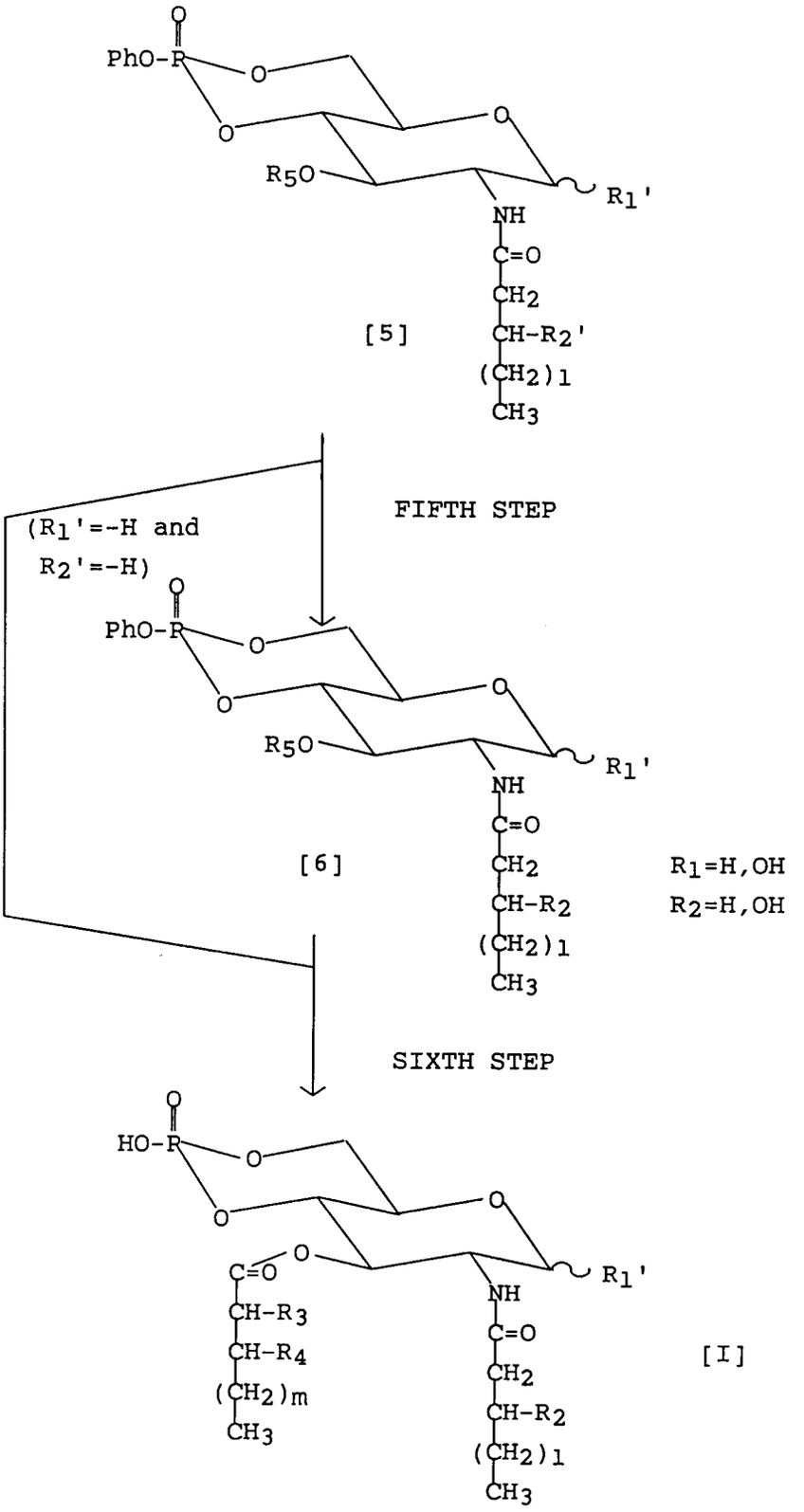


THIRD STEP



[4]

FOURTH STEP



Description of said flow 1 is in detail as follows:

<the first step>

The known compound [1] derived from D-glucosamine (see Japanese Patent Disclosure No. 197582/86) is amidated to form an amide compound [2]. This procedure is performed by making the compound [1] to react with a fatty acid compounds whose hydroxyl group at 3-position is protected with 2-(trimethylsilyl)-ethoxymethyl group (-SEM group) or with straight-chain fatty acid compound having no hydroxy group, in an inert solvent such as dichloromethane, in the presence of a condensation agent such as dicyclohexylcarbodiimide (DCC) and 1-ethyl-3(3-dimethylaminopropyl)-carbodiimide hydrochloride (WSC•HCl).

<the second step>

The compound [2] obtained in the first step is caused to react with an acylating agent thereby acylating the hydroxyl group at the 3-position of the ring in order to obtain a compound [3]. Examples of the acylating compound are α- or β-alkyl fatty acid, α- or β-acyloxy fatty acid and α- or β-alkoxy fatty acid (R_5OH). This step is performed in a solvent such as dichloromethane in the presence of dimethylaminopyridine (DMAP) of catalytic amount, and a condensation agent such as DCC and WSC•HCl.

<the third step>

The compound [3] obtained in the second step is hydrolyzed with an acid such as acetic acid solution, in order to eliminate the protection groups at the 4- and 6-position, yielding a compound [4].

<the fourth step>

The compound [4] is made to react with phenyl dichlorophosphate in an inert solvent such as dichloromethane in the presence of a base such as pyridine and DMAP in order to obtain a compound [5].

<the fifth step>

This step is performed in order to eliminate protection groups at hydroxy groups when R_1' and/or R_2' are protected hydroxy groups. Therefore, when both R_1' and R_2' are hydrogen atoms, this step is not required. When both R_1' and R_2' are protected hydroxy groups, both protection groups may be simultaneously eliminated, or they may be separately eliminated in a stepwise manner.

The elimination step can be performed in various known manners. For example, when the R_1' and/or R_2' of the compound [5] are -OSE, the compound [5] is dissolved in an inert solvent such as dichloromethane, and an acid such as boron trifluoride etherate ($BF_3.OEt_2$) or a fluoride ion generating agent such as tetrabutylammonium fluoride is added to the solution in order to easily eliminate the protection groups.

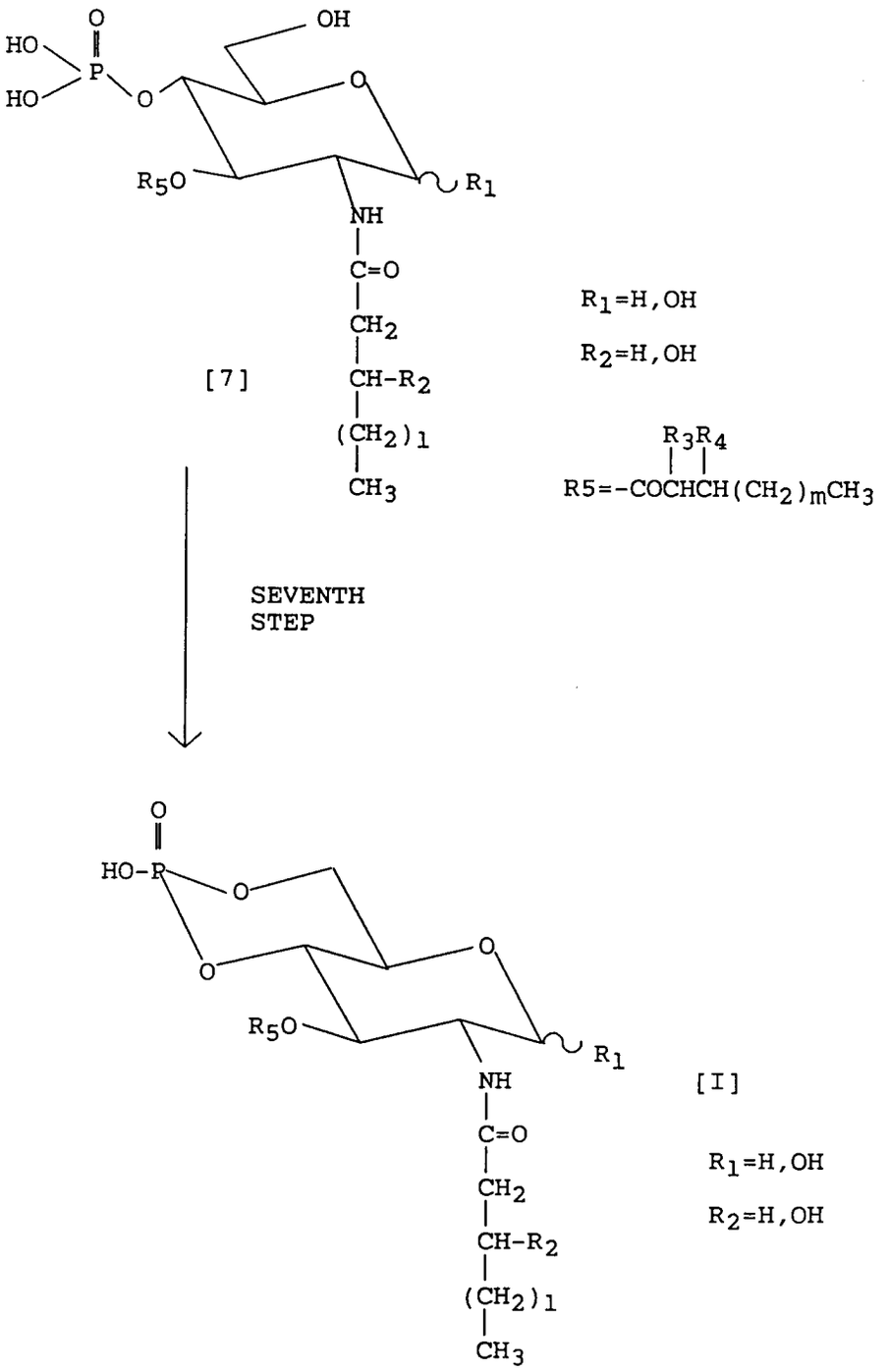
It is noted that the protection groups in the R_1' and/or R_2' are not restricted to -OSE described above, and they may be, for example, benzyl groups (-Bn group). When they are benzyl groups, they are easily eliminated through catalytic hydrogenation in the presence of a catalyst such as platinum and palladium.

<the sixth step>

The compound [6] is hydrogenated over platinum dioxide (PtO_2), etc. in a solvent such as ethanol, methanol, and acetic acid to afford an objective compound [I].

This objective compound [I] can be also prepared according to the following reaction from a lipid A analogue obtained in a known manner.

FLOW 2



This flow 2 comprises the following seventh step.

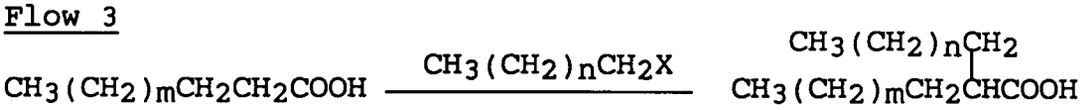
<the seventh step>

A compound [7] (for example, see Japanese Patent Disclosure No. 62888/90) is made to react with a condensation agent such as DCC and WSC.HCl in a solvent such as tetrahydrofuran(THF), dichloromethane, and chloroform. By this reaction, the compound [7] is cyclized by intramolecular condensation to afford the objective compound [I].

Among α- or β- alkylated fatty acid, α- or β-acyloxylated fatty acid, and α- or β-alkoxylated fatty acid, some are known, and others are easily prepared from known compounds. Examples of methods for producing these substituents are as follows:

[Method for Producing α-alkyllated fatty acid]

Flow 3

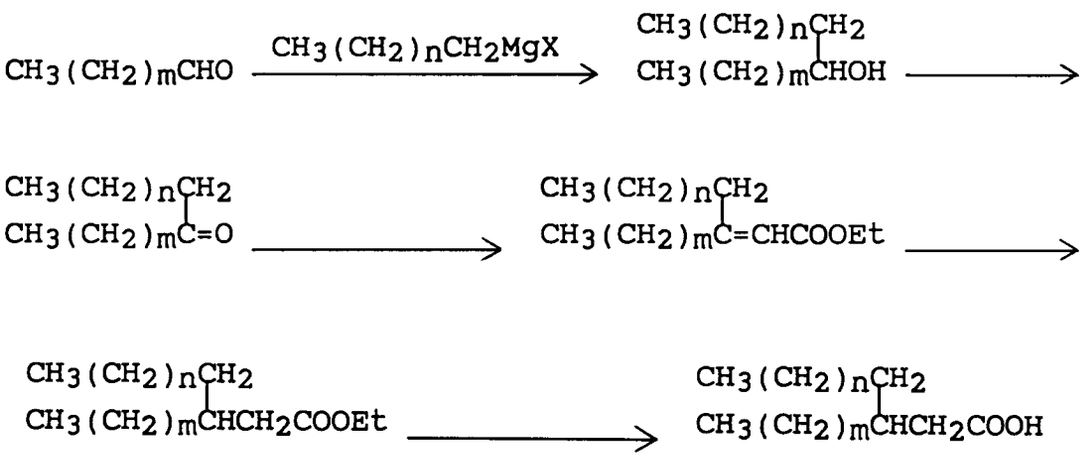


wherein X indicates halogen.

This reaction is performed in aprotic solvents such as tetrahydrofuran (THF) containing hexamethylphosphoric triamide (HMPA), etc.. First, a straight chain carboxylic acid having the corresponding number of carbons is added with two equivalents of strong base such as lithium diisopropylamide (LDA) in order to form dianion of the carboxylic acid. Next, the dianion is made to react with straight chain alkylhalide having the corresponding number of carbons to obtain the α-alkylated fatty acid.

[Method for Producing β-alkylated fatty acid]

Flow 4



Straight chain alkyl halide having the corresponding number of carbons is made to react with metal magnesium in an aprotic solvent such as THF in order to form Grignard reagent. The straight chain aldehyde having the corresponding number of carbons are made to react with the Grignard reagent to yield a secondary alcohol. This alcohol is oxidized with an oxidizing agent such as pyridinium chlorochromate (PCC) and Jones reagent in an inert solvent such as dichloromethane to form a ketone.

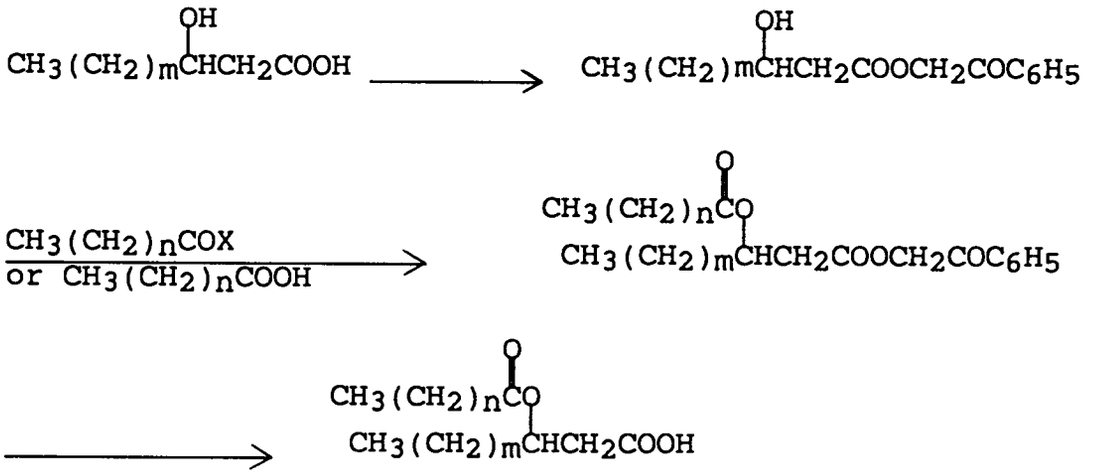
Separately, triethyl phosphonoacetate is added with base such as sodium hydride in order to form carboanion.

The Wittig reaction of the carboanion and the aforementioned ketone yields α, β-unsaturated ester.

Next, this ester is subjected to hydrogenation in a solvent such as ethyl acetate in the presence of palladium carbon to form saturated ester. Finally, this ester is hydrolyzed in a solvent such as aqueous ethanol in the presence of base such as potassium hydroxide to obtain β-alkylated fatty acid.

[Method for Producing α- or β-acyloxylated fatty acid]

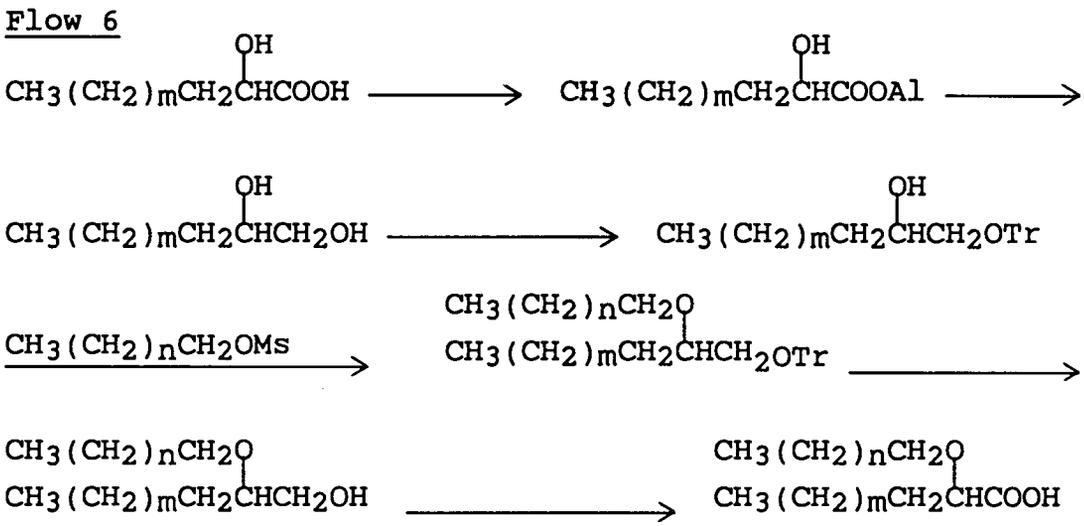
Flow 5



2- or 3-hydroxycaroboxlyic acid of straight chain having the corresponding number of carbons (for example, 3-hydroxycarboxylic acid is shown in the flow 5) is acylated as follows. First, the hydroxycarboxylic acid is reacted with phenacyl bromide in a solvent such as ethyl acetate in the presence of a base such as triethylamine to form phenacyl ester. The hydroxy group at the 2- or 3-position of the phenacyl ester is acylated by being reacted with acid chloride having the corresponding number of carbons in the presence of a base such as pyridine, or with straight chain carboxylic acid having the corresponding number of carbons in the presence of a condensation agent such as DCC and WSC•HCl in an inert solvent such as dichloromethane. Next, the acylated phenacyl ester is treated with zinc powder and acetic acid in order to eliminate a phenacyl group. As the result, α- or β-acyloxylated fatty acids are obtained.

[Method for Producing α- or β-alkoxylated fatty acid]

Flow 6



wherein Aℓ indicates an alkyl group such as methyl group and ethyl group, Tr indicates a protection group such as trityl group for a hydroxyl group, and Ms indicates a mesyl group or tosyl group, etc..

2- or 3-hydroxycaroboxylic acid having the corresponding number of carbons (for example, 2-hydroxycarboxylic acid is shown in the flow 6) is esterified with methyl iodide, ethyl iodide or the like in an aprotic solvent such as benzene in the presence of a base such as 1,8-diazabicyclo[5,4,0]7-undecene (DBU). The obtained ester is reduced with a reducing agent such as lithium aluminium hydride in a solvent such as

THF to yield diol. Next, of OH groups in the obtained diols, only primary OH group is selectively protected with a protection group such as trityl group. The protected alcohol is reacted with straight chain alcohol which has the corresponding number of carbons and which is mesylated or tosylated, in an aprotic solvent such as THF, in the presence of a base such as potassium hydride or sodium hydride and a phase transfer catalyst such as tetra-n-butylammonium iodide, to introduce an alkoxy substituent. Next, the protection group (trityl group) at the primary hydroxy group is eliminated by using an acid such as p-toluensulfonic acid. Finally, the obtained alcohol is oxidized with an oxidizing agent such as Jones reagent and PCC in order to obtain β-alkoxy substituted fatty acid.

Here is the description of pharmaceutical applications of the compounds according to the present invention.

The compound of the general formula [I] is generally administered systemically or topically, and orally or parenterally.

Although administered dose varys with age, weight, and symptom of a patient in question, therapeutic effect desired, administration route, treatment period, etc., 0.01-100mg of the compound is generally administered orally or parenterally to an adult once to several times a day.

Solid compositions prepared to be orally administered according to this invention include tablets, powder, granules, etc.. These solid compositions are obtained by mixing at least one active substance with at least one inert diluent or dispersing agent. Examples of the diluents or dispersing agents include lactose, mannitol, glucose, hydroxypropylcellulose, crystalline cellulose, starch, polyvinylpyrrolidon, magnesium alumlno-metasilicate, etc.. Other than these diluents or dispersing agents, absorbents such as anhydrous silica powder, etc. may be mixed with the compound [I]. Further, the solid compositions may contain additives other than inactive diluents, according to a general method.

The tablets or pills stated above may be coated, if desired, with acid soluble films or enteric coating films such as saccharose, gelatin, hydroxypropylcellulose and hydroxypropylmethylcellulose phthalate. Some tablets or pills may be coated, if desired, with two or more these films. Also powder or granules may be encapsulated within capsules made of gelatin, ethylcellulose, etc..

Examples of liquid compositions for oral administration include pharmaceutically acceptable emulsion, solution, suspension, syrup, erixil, etc.. These liquid compositions may contain inert diluents generally utilized, e.g., purified water, ethanol, vegetable oils, emulsifying agent. Further, auxiliary agents such as moisturing agents or suspending agents, edulcorants, flavouring agents, perfumes, and antiseptics may be contained in the compositions.

Injectable preparations for parenteral administration may contain sterilized aqueous or non-aqueous solvents, solubilizing agents, suspending agents, and emulsifying agents. Examples of the aqueous solvents, solubilizing agents, and suspending agents include distilled water for injection, saline solution, cyclodextrin and its derivatives, organic amines such as triethanolamine, diethanolamine, monoethanolamine, and triethylamine, and inorganic alkalines.

Examples of the non-aqueous solvent include propyleneglycol, polyethyleneglycol, vegetable oils such as olive oil, and alcohols such as ethanol. Examples of non-aqueous solubilizing agents include surfactants (which forms mixed miscells) such as polyoxyethylene hydrogenated castor oil, and sucrose fatty acid ester, lecithin, and hydrogenated lecithin (which forms liposomes), etc.. Emulsion preparations are also included in the non-aqueous solution preparation, which are obtained by using non-aqueous solvent such as vegetable oils with emulsifying agents such as lecithin, polyoxyethylene hydrogenated castor oils, and polyoxyethylenepolyoxypropyleneglycol.

Examples of other compositions which are adminstered via any route other than per os are topical solutions, liniments such as ointments, suppositories, pessaries, etc., each of which contains at least one active substance and is prepared according to the disclosed method.

Hereinafter are described pharmacological actions of the compounds according to this invention by way of experimental examples. The compounds according to this invention have showed significant effects for various tests such as IL-1-producing activity, and also showed low toxicities for tests such as local Schwartzman reaction, and pyrogenicity. Some activities are stated as follows.

Experimental Example 1 (O_2^- production stimulating activity in neutrophils)

O_2^- production stimulating activity in neutrophils was evaluated utilizing the following experimental system [see J. Exp. Med., 160, 1656-1671. (1984)]. To the peritoneal cavity of C3H/HeN mouse (male, 8-9 week-aged), physiological saline containing 0.2% (w/v) casein was administered. Three hours later, peritoneal exudate cells (90% or more of which are neutrophils) were collected. These cells (1.7×10^6 cells/mℓ/tube) were incubated in the presence of the compound (10 μg/mℓ) according to this invention at

37°C for 60 minutes. After addition of 80 μM of cytochrome C and 0.1 μM of formyl-methionyl-leucylphenylalanine (FMLP), the mixture was incubated in the presence of or in the absence of superoxide dismutase (SOD) at 37°C for 10 minutes. Then, SOD-inhibitable cytochrome C reduction was estimated from the difference between absorbances at 550 nm and 541.7 nm, and from molar absorption coefficient (16.5×10^3). O_2^- production-stimulating activity was shown in Stimulation % in the following formula.

$$\text{Stimulation (\%)} = \frac{\text{the amount of } O_2^- \text{ produced in the presence of the compound according to the invention}}{\text{the amount of } O_2^- \text{ produced in the absence of the compound according to the invention}} \times 100-100$$

The compound according to the present invention showed the activity in the following Table 1. Control compound in the Table 1 is 2-deoxy-2[(3R)-3-hydroxytetradecanamide]-4-O-phosphono-3-O-[(3R)-3-tetradecanoyloxytetradecanoyl]-D-glucopyranose (GLA-60).

Table 1

Compound	Stimulation (%)	
	Experiment 1	Experiment 2
No compound	0	0
Control	60	60
Example 1	55	--
Example 4	--	55

Experimental Example 2 (TNF-producing activity)

TNF-producing activity was evaluated utilizing the following experiment system.

The first stimulating agent, 5% Corynebacterium parvum suspension (0.2 mℓ physiological saline solution) was intravenously administered to ICR mouse (female, 6-7 week-aged). Nine days later, the second stimulating agent, the compound of this invention was intravenously administered to the same mouse at 10 μg/mouse. In 90 minutes, 0.5 - 1 mℓ of blood was taken from the retro orbital plexus. The obtained blood was allowed to clot at room temperature for five to six hours, and centrifuged at 7200 × g for five minutes to separate serum. The obtained serum was incubated at 56°C for 30 minutes for inactivation before use in the following experiment.

TNF activity in the serum was measured with cytotoxicity assay using L929 cells. L929 cells were prepared in concentration of 6×10^4 cells/well (0.1 mℓ) RPMI 1640 medium containing 10% FBS (fetal bovine serum) and 2 μg/mℓ actinomycin D in 96-well plates. Serial dilution of obtained serum in RPMI 1640 medium containing 10% FBS was added to each well in the plate (0.1 mℓ/well). After a 48 hr incubation at 37°C, the viable cells were fixed with methanol. These cells were then stained with 0.2% crystal violet, and the dye was extracted with 1% SDS (sodium dodecyl sulphate). Next, absorbance at 550 nm was measured. Finally, cytotoxicity ratio (%) was calculated according to the following formula, and the reciprocal of dilution of the serum showing 50% cytotoxicity was determined for TNF titer in serum (U/mℓ).

Cytotoxicity (%)
= [OD_{550} (medium alone) - OD_{550} (serum obtained by administering compounds of the invention)] × 100/OD_{550} (medium alone)

The compounds of this invention revealed activities shown in the following Table 2.

Table 2

Compound	The Amount of TNF in the Serum (U/mℓ)	
	Experiment 1	Experiment 2
No compound	< 10	< 10
Control	158000	80000
Example 1	133000	--
Example 2	--	102000

Experimental Example 3 (Mitogen Activity)

Mitogen activity of the compounds according to the present invention was evaluated by utilizing the following experimental system [see Eur.J.Immunol., 14, 109-114. (1984)].

The spleen of C3H/HeN mice (male, 6-10-week age) were isolated in an aseptic manner. The spleen tissue was loosened in Dulbecco's modified Eagle medium (DMEM) and then subjected to a stainless mesh in order to filter the spleen cells. Next, erythrocytes contained in the collected cells were made to hemolyzed, and the obtained cells were suspended in RPMI 1640 medium containing 5% FBS for use.

Evaluation of mitogen activity of the compounds according to the present invention was made by measuring the amount of ^{3}H-thymidine incorporated into the cells during the culture of the cells which were treated with the compounds according to the present invention. First, the spleen cells were transferred to a 96-well plate at 5×10^5/well (100 μℓ). To each well, the compounds according to the present invention of a given concentration (100 μℓ) was added, and the obtained solution in each well was cultured under 5% CO_2 at 37°C for 48 hours. After that, ^{3}H-thymidine was added at I μCi/well (50 μℓ), followed by a culture for four hours. The obtained cells were washed with phosphate buffered saline (PBS), and the amount of ^{3}H-thymidine incorporated into the cells (the amount of radioactivity) was determined by a liquid scintillation counter. The result was shown by calculating the following stimulation index.

$$\text{Stimulation Index} = \frac{\text{The Radioactive Amount when the compound is added to the medium (cpm)} - \text{The Radioactive Amount when the medium only is added (cpm)}}{\text{The Radioactive Amount when the medium only is added (cpm)}}$$

The compounds according to the present invention showed the following activities.

Table 3

Compound	Stimulation Index	
	Experiment 1	Experiment 2
No compound	0	0
Control	15.8	8.4
Example 1	32.1	--
Example 4	--	20.7

Experimental Example 4 (Colony Stimulating Factor-Inducing Activity)

By utilizing the following experimental example, in vivo colony stimulating factor (CSF) inducing activity of the compounds according to the present invention was evaluated [see Immunology, 21, 427-436. (1971)].

5 μg of the present compounds according to the present invention were administered to the caudal vein of C57BL mice (male, 8-10-week age). After six hours, the blood was sampled from the plexus venous orbitalis of said mice. This blood was allowed to stand at 4°C for two hours for sufficient coaggulation, and then centrifuged at 1500 × g. The resultant supernatant solution was collected for use as a CSF-containing serum sample.

Separately, from the femora of mice which were the same series as the mice used for sampling the serum, the bone marrow cells were sampled. Specifically, both ends of the femora isolated in an aseptic manner were cut, and an injection needle was inserted to one end to aspirate the bone marrow cells into a culture solution (DMEM). The obtained cell suspension was sufficiently stirred, washed with the culture solution several times, and suspended in the culture solution again.

Next, the cell culture prepared as said was adjusted to a final concentration of 10^5/mℓ by utilizing a medium (DMEM) containing 0.3% agar, 25% horse serum, and 50 μM 2-mercaptoethanol. To this solution, 0.1mℓ of said serum sample which had been diluted to 1/3 with said DMEM medium was added, and the obtained solution was transferred to a culture plate of 35mm diameter. Then, the resultant culture solution was cultured under 7% CO_2 at 37°C for seven days to form colonies. Such colonies as containing at least 20 cells which are not separated so far were counted, and the numbers thus obtained were taken CSF inducing activity of the compounds according to the present invention.

This activity was shown in the following Table 4.

Table 4

Compound	The Number of Colony Formed/ The number of Bone Marrow Cells (10^5)	
	Experiment 1	Experiment 2
No compound	0	0
Control	89	53
Example 1	153	--
Example 4	--	66

Experimental Example 5 (lethal toxicity in galactosamine-sensitized mice)

Lethal toxicity in galactosamin-sensitized mice was evaluated by utilizing the following experiment system [see J.Biochem., 98, 395-406. (1985)].

To C57BL mouse (male, 7-week aged), 10 mg/mouse of D-galactosamine/HCℓ was intraperitoneally administered. Immediately after that, the compound of this invention was intravenously administered. After these administrations, general conditions of the mouse were observed every one hour for seven hours, and every day from the following day to the seventh day.

The compound of this invention showed lethal toxicity as in the following Table 5;

Table 5

Compound	LD_{50} (galactosamine load)(μg/kg)
Lipid A	0.3
Control	3.0
Example 1	31.3
Example 4	71.1
* Synthetic lipid A (LA-15-PP, 506, manufactured by Daiichi Kagaku Yakuhin)	

[Best Mode of Carrying Out the Invention]

Hereinafter is the detailed description of methods for producing the final objective compound [I] and its intermediates [1] to [7] by way of examples. However, it should be understood that the present invention is not restricted to these examples. For example, the following compounds are also included in the present invention.

- 1,5-anhydro-2-deoxy-2-dodecanamido-3-O-{(2RS)-2-hexadecyloxydodecanoyl}-4,6-O-hydroxyphosphoryl-D-glucitol
- 1,5-anhydro-2-deoxy-2-dodecanamido-3-O-{(3RS)-3-hexadecyloxydodecanoyl}-4,6-O-hydroxyphosphoryl-D-glucitol
- 1,5-anhydro-2-deoxy-3-O-{(3RS)-3-dodecylhexadecanoyl}-2-hexadecanamido-4,6-O-hydroxyphosphoryl-D-glucitol
- 1,5-anhydro-2-deoxy-3-O-{(2RS)-2-dodecyloxyoctadecanoyl}-2-{(3R)-3-hydroxydodecanamido}-4,6-O-hydroxyphosphoryl-D-glucitol
- 1,5-anhydro-3-O-{(3RS)-3-decyloctadecanoyl}-2-deoxy-2-{(3RS)-3-hydroxyhexadecanamido}-4,6-O-hydroxyphosphoryl-D-glucitol
- 1,5-anhydro-2-deoxy-2-dodecanamido-3-O-{(2RS)-2 dodecyloxyoctadecanoyl}-4,6-O-hydroxyphosphoryl-D-glucitol
- 1,5-anhydro-3-O-{(3RS)-3-decyloctadecanoyl)-2-deoxy-2-hexadecanamido}-4,6-O-hydroxyphosphoryl-D-glucitol
- 2-deoxy-3-O-{(2RS)-2-dodecylhexadecanoyl}-4,6-O-hydroxyphosphoryl-2-tetradecanamido-D-glucopyranose
- 2-deoxy-4,6-O-hydroxyphosphoryl-2-tetradecanamido-3-O-{(2RS)-2tetradecanoyloxytetradecanoyl}-D-glucopyranose
- 2-deoxy-3-O-{(2RS)-2-dodecyloxyhexadecanoyl}-4,6-O-hydroxyphosphoryl-2-tetradecanamido-D-glucopyranose
- 2-deoxy-3-O-{(3RS)-3-dodecylhexadecanoyl}-4,6-O-hydroxyphosphoryl-2-tetradecanamido-D-glucopyranose
- 2-deoxy-4,6-O-hydroxyphosphoryl-2-tetradecanamido-3-O-{(3RS)-3-tetradecanoyloxytetradecanoyl}-D-glucopyranose
- 2-deoxy-3-O-{(3RS)-3-dodecyloxyhexadecanoyl}-4,6-O-hydroxyphosphoryl-2-tetradecanamido-D-glucopyranose
- 2-deoxy-3-O-{(3RS)-3-dodecyloxyhexadecanoyl}-2-{(3RS)-3-hydroxyoctadecanamido}-4,6-O-hydroxyphosphoryl-D-glucopyranose

Relations of the compound [I] according to the present invention, intermediates [1] to [7] for producing the compound [I], and compound numbers are shown in the following Table 6.

Table 6

R_1	R_2	l	R_3	R_5	R_4	m	COMPOUND NUMBER								Example
							1	2	3	4	5	6	7	[I]	
H	OH	10	$-OCO(CH_2)_{12}CH_3$		H	10	1a	2a	3a	4a	5a	6a		A	1
H	OH	8	$-OCO(CH_2)_{10}CH_3$		H	12	1a	2b	3b	4b	5b	6b		B	2
H	OH	12	$-OCO(CH_2)_{14}CH_3$		H	8	1a	2c	3c	4c	5c	6c		C	3
H	OH	10	$-CH_2(CH_2)_{12}CH_3$		H	10	1a	2a	3d	4d	5d	6d		D	4
H	OH	8	$-CH_2(CH_2)_{14}CH_3$		H	10	1a	2b	3e	4e	5e	6e		E	5
H	OH	12	$-CH_2(CH_2)_{14}CH_3$		H	8	1a	2c	3f	4f	5f	6f		F	6
H	OH	10	H		$-OCO(CH_2)_{12}CH_3$	10	1a	2a	3g	4g	5g	6g		G	7
H	OH	10	H		$-CH_2(CH_2)_{12}CH_3$	10	1a	2a	3h	4h	5h	6h		H	8
H	H	10	$-CH_2(CH_2)_{10}CH_3$		H	10	1a	2i	3i	4i	5i			I	9
H	OH	10	$-OCH_2(CH_2)_{12}CH_3$		H	10	1a	2a	3j	4j	5j	6j		J	10
OH	OH	10	$-OCO(CH_2)_{12}CH_3$		H	10							7k	K	11
OH	OH	10	$-CH_2(CH_2)_{12}CH_3$		H	10							7l	L	12
OH	OH	10	H		$-OCO(CH_2)_{12}CH_3$	10							7m	M	13
OH	OH	10	H		$-CH_2(CH_2)_9CH_3$	13							7n	N	14

Example 1
1,5-Anhydro-2-deoxy-4,6-O-hydroxyphosphoryl-2-{(3R)-3-hydroxytetradecanamido}-3-O-{(2R)-2-tetradecanoyloxytetradecanoyl}-D-glucitol; (Compound A)

(the first step)
1,5-Anhydro-2-deoxy-4,6-O-isopropyriden-2-[(3R)-3-(2-(trimethylsilyl)ethoxymethoxy}tetradecanamido]-D-glucitol; (Compound 2a)

2-Amino-1,5-anhydro-2-deoxy-4,6-O-isopropyriden-D-glucitol(1a) (5.8g), (R)-3-{2-(trimethylsilyl)-ethoxymethoxy)tetradecanoic acid (10.7g), and WSC•HCl (11g) were dissolved in dichloromethane (44mℓ), and the resultant solution was stirred under ice-cooling for reaction. The reaction was monitored utilizing a silica gel thin layer chromatography (chloroform:methanol = 20:1). After the reaction went to completion, the mixture was diluted with dichloromethane, washed with water, and dried with anhydrous magnesium sulfate. The obtained solution was evaporated to remove the solvent, and the resultant residue was purified by a silica gel column chromatography (chloroform:methanol = 100:1). A colourless crystal compound (2a) (14g, yield: 88%) was obtained.

[α]D:	-6.90° (c = 1.10, $CH_2Cℓ_2$)
m. p.:	61.0 - 62.0°C
IR(nujol)cm^{-1}:	3450, 3280, 1640, 1550, 1460, 1380, 860 - 835
^{1}H-NMR(300MHz)δTMS $CDCℓ_3$:	0.03(9H, s, Me_3Si), 0.85 - 0.97(5H, m, CH_2TMS, -Me), 1.20 - 1.60(20H, m, $-CH_2-$), 1.43, 1.52(6H, each s, $-CMe_2$), 2,38, 2,48(2H, AB part of ABX, J_{AB} = 14,9 Hz, J_{AX} = 6.6 Hz, J_{BX} = 4.0 Hz, $-CH_2CO-$), 3.22(2H, m, H-1, H-5), 3.44(1H, brs, -OH), 3.54 - 3.65(4H, m, H-1, H-4, $-CH_2CH_2$TMS), 3.72(1H, t, J = 10.5 Hz, H-6), 3.87 - 3.92(2H, m, H-6, CH-OSEM), 4.01 - 4.09(2H, m, H-2, H-3), 4.67, 4.75(2H, AB, J_{AB} = 6.6 Hz, $-OCH_2O-$), 6.47(1H, d, J = 7.0Hz, NH)

(the second step)
1,5-Anhydro-2-deoxy-4,6-O-isopropyriden-3-O-{(2R)-2-tetradecanoyloxytetradecanoyl)-2-[(3R)-3-(2-(trimethylsilyl)ethoxymethoxy}-tetradecanamido]-D-glucitol; (Compound 3a)

The compound 2a (1.73g), (R)-2-tetradecanoyloxytetradecanoic acid (1.4g), WSC•HCl (1.19g), and DMAP (189mg) were dissolved in dichloromethane (14.7mℓ), and the obtained solution was stirred for three hours for reaction. The reacted solution was diluted with dichloromethane, washed with water, dried with anhydrous magnesium sulfate, and concentrated under a reduced pressure. The obtained residue was purified by a silica gel column chromatography (n-hexane: ethyl acetate = 3:1) to obtain an amorphous compound (3a) (2.53g, yield: 82.2%).

[α]D:	+9.3° (c = 1.1, $CHCℓ_3$)
IR(film)cm^{-1}:	3386, 2928, 2858, 1746, 1657, 1543, 1466, 1379
^{1}H-NMR(300MHz)δTMS $CDCℓ_3$:	0.02(9H, s, Me_3Si), 0.79 - 0.96(11H, m, -Me, CH_2TMS), 1.12 - 1.83(64H, m, $-CH_2-$), 1.35, 1.45(6H, each s, $>CMe_2$), 2.18 - 2.47(4H, m, $-COCH_2-$), 3.09 - 3.29(2H, m, H-1, H-5), 3.48 - 3.98(6H, m, H-1, H-4, H_2-6, $-CH_2CH_2$TMS), 4.04 - 4.26(2H, m, H-2, CHOSEM), 4.62 - 4.68(2H, AB, J_{AB} = 6.8 Hz, $-OCH_2O-$), 4.86(1H, t, J = 6.3 Hz, >CHOCO-), 4.93(1H, t, H-3), 5.99(1H, d, J = 7.3 Hz, NH)

(the third step)
1,5-Anhydro-2-deoxy-3-O-{(2R)-2-tetradecanoyloxytetradecanoyl}-2-[(3R)-3-{2-(trimethylsilyl)-ethoxyemthoxy}-tetradecanamido]-D-glucitol; (Compound 4a)

The compound 3a (2.5g) was dissolved in 95% acetic acid solution (32mℓ), and the obtained solution was stirred in a water bath at 50°C for five hours to be reacted. The reacted solution was then diluted with toluene and concentrated under reduced pressure. The obtained residue was purified by a silica gel column chromatography (chloroform: methanol = 100:1) to obtain an amorphous compound (4a) (1.6g, yield: 67.7%).

[α}D:	+12.6° (c = 1.65, $CHC\ell_3$)
IR(film)cm^{-1}:	3550 - 3150, 2926, 2858, 1742, 1655, 1543, 1460, 1365
^{1}H-NMR(300MHz)δTMS $CDC\ell_3$:	0.02(9H, s, Me_3Si), 0.80 - 0.99(11H, -Me, CH_2TMS), 1.17 - 1.89(64H, m, $-CH_2-$), 2.20 - 2.44(4H, m, $-COCH_2-$), 2.85(1H, brs, -OH), 3.14(1H, t, J = 12.3 Hz, H-1), 3.25 - 3.37(1H, m, H-5), 3.48 - 3.68(3H, m, H-4, CH_2CH_2TMS), 3.70 - 3.81(1H, m, H-6), 3.82 - 3.76(2H, m, H-1, H-6) 4.01 - 4.20(2H, m, H-2, CHOSEM), 4.64 - 4.70(2H, AB, J_{AB} = 6.9 Hz, $-OCH_2O-$), 4.82(1H, t, J = 6.5 Hz, >CHOCO-), 4.89(1H, t, J = 10.1 Hz, H-3), 6.13(1H, d, J=7,4 Hz, NH)

(the fourth step)

1,5-Anhydro-2-deoxy-4,6-O-phenoxyphosphoryl-3-O-{(2R)-2-tetradecanoyloxytetradecanoyl}-2-[(3R)-3-{2-(trimethylsilyl)ethoxymethoxy} tetradecanamido]-D-glucitol; (Compound 5a)

The compound 4a (1.6g) was dissolved in pyridine (1.6mℓ) and dichloromethane (3.3mℓ). To the resultant solution, phenyl dichlorophosphate (0.41mℓ) was dropwise added under ice-cooling, followed by stirring for reaction. After four hours, the reacted solution was diluted with chloroform, washed with water, dried with anhydrous magnesium sulfate, and evaporated under a reduced pressure to remove the solvent. The resultant residue was purified by a silica gel column chromatography (chloroform) to obtain an amorphous compound 5a (437mg, yield: 23.2%).

IR(film)cm^{-1}:	3306, 2926, 2858, 1744, 1655, 1595, 1460, 1379 1207, 944, 690
^{1}H-NMR(300MHz)δTMS $CDC\ell_3$:	0.01, 0.02(9H, each s, $SiMe_3$) 0.80 - 1.00(11H, m, -Me, $-CH_2TMS$), 1.14 - 1.69(64H, m, $-CH_2-$), 2.20 - 2.50(4H, m, $-COCH_2-$), 3.18 - 3.32(1H, m, H-1), 3.49 - 3.79(3H, m, H-5, $-CH_2CH_2TMS$), 3.88 - 4.00(1H, m, >CH-OSEM), 4.06 - 4.56(5H, m, H-1, H-2, H-4, H_2-6), 4.63 - 4.70(2H, AB, J_{AB} = 11.5 Hz, $-OCH_2O-$), 4.72 - 4.88(1H, m, >CHOCO-), 5.12, 5.16(1H, each t, J = 9.6 Hz, J = 7.1 Hz, H-3), 6.00, 6.03(1H, each d, J = 6.9 Hz, J = 7.1 Hz, NH), 7.11 - 7.44(5H, m, Ph)

(the fifth step)

1,5-Anhydro-2-deoxy-2-{(3R)-3-hydroxytetradecanamido}-4,6-O-phenoxyphosphoryl-3-O-{(2R)-2-tetradecanoyloxytetradecanoyl}-D-glucitol; (Compound 6a)

The compound 5a (437mg) was dissolved in dried dichloromethane (8.7mℓ). To the solution, boron trifluoride etherate (0.44mℓ) was dropwise added under ice-cooling, followed by stirring for thirty minutes for reaction. The reacted solution was diluted with dichloromethane, and washed with water, aqueous sodium bicarbonate solution, and water in this order. The obtained solution was then dried with anhydrous magnesium sulfate, and evaporated under a reduced pressure to remove the solvent. The obtained residual was purified by a silica gel column chromatography (chloroform: methanol = 100:1) to afford an amorphous

compound (6a) (249mg, yield: 64.7%).

IR(film)cm^{-1}:	3320, 2924, 2858, 1742, 1657, 1524, 1207
^{1}H-NMR(300MHz)δTMS $CDCl_3$:	0.88(9H, t, J = 6.3 Hz, Me)
	1.13 - 1.76(64H, m, $-CH_2-$),
	2.21 - 2.49(4H, m, $-COCH_2-$),
	3.21 - 3.42(2H, H-1, OH),
	3.53 - 3.63, 3.69 - 3.80(1H, each m, H-5),
	3.85 - 3.96(1H, m, >CH-OH),
	4.01 - 4.56(5H, m, H-1, H-2, H-4, H_2-6),
	4.70 - 4.85(1H, m, >CHOCO-),
	5.19 - 5.32(1H, m, H-3),
	6.50, 6.60(1H, each d, J = 8.5 Hz, J = 7.9 Hz, NH),
	7.11 - 7.43(5H, m, Ph)

(the sixth step)

The compound 6a (50mg) was dissolved in acetic acid (5mℓ). The solution was added with platinum dioxide (20mg), and stirred in H_2 atmosphere under pressure (1.5kg/cm^2) for two hours for reaction. The reacted solution was then filtered to remove the catalyst, and the filtrate was concentrated under a reduced pressure. The obtained residue was suspended in 1,4-dioxane, and the obtained suspension was lyophilized to obtain a white powder compound (A) (45mg, yield: 97.7%).

^{1}H-NMR:	Hydrogen signals on the benzene ring completely disappeared.
m. p.:	103.6 - 104.5°C (decomp.)
IR(nujol)cm^{-1}:	3350, 1738, 1657, 1540
SI-MS:	887$(M-H)^-$

Example 2

1,5-Anhydro-2-deoxy-3-O-{(2RS)-2-dodecanoyloxyhexadecanoyl}-2-{(3R)-3-hydroxydodecanamido)-4,6-O-hydroxyphosphoryl-D-glucitol; (Compound B)

(the first step)

1,5-Anhydro-2-deoxy-4,6-O-isopropyriden-2-[(3R)-3-{2-(trimethylsilyl)ethoxymethoxy}dodecanamido]-D-glucitol; (Compound 2b)

A compound 2b was formed (1.7g, yield: 57.3%) according to the same manner as that for the compound 2a, except that (R)-3-{2-(trimethylsilyl) ethoxymethoxy}dodecanoic acid (2.1g) was used.

[α]D:	-5.17° (c = 0.97, $CHCl_3$)
m. p.:	91 - 94°C
1R(KBr)cm^{-1}:	3488, 2860, 1466, 1251, 1203, 1104
^{1}H-NMR:	the same as that for the compound 2a except for a $-CH_2-$ integration value

(the second step)

1,5-Anhydro-2-deoxy-3-O-{(2RS-2-dodecanoyloxyhexadecanoyl)-4,6-O-isopropyriden-2-[(3R)-3-{2-(trimethylsilyl)ethoxymethoxy}dodecanamido]-D-glucitol; (Compound 3b)

A compound 3b was formed (1.6g, yield: 89.0%) according to the same manner as for the compound 3a, except that the compound 2b (1.0g) and (RS)-2-dodecanoyloxyhexadecanoic acid (800mg) were used.

IR:	the same as that for the compound 3a
^{1}H-NMR(300MHz)δTMS $CDCl_3$:	0.02(9H, s, $-SiMe_3$),
	0.86 - 0.94(11H, m, -Me, $-CH_2$TMS),
	1.19 - 1.35(60H, m, $-CH_2-$),
	1.35, 1.37, 1.45, 1.47(6H, each s, $>CMe_2$),
	2.23 - 2.46(4H, m, $-COCH_2-$),
	3.11 - 3.29(2H, m, H-1, H-5),
	3.52 - 3.99(6H, m, H-2, H-4, H_2-6, $-OCH_2CH_2$TMS),
	4.06 - 4.23(2H, m, H-2, >CHOCO),
	4.95(1H, t, H-3),
	6.01 - 6.05(1H, m, NH),

(the third step)
1,5-Anhydro-2-deoxy-3-O-{(2RS)-2-dodecanoyloxyhexadecanoyl}-2-[(3R)-3-{2-(trimethylsilyl)-ethoxymethoxy}dodecanamido]-D-glucitol; (Compound 4b)

Compound 4b was obtained (1.0g, yield: 52.8%) according to the same manner as that for the compound 4a, except that the compound 3b (2.0g) was used.

IR:	the same as that for the compound 3a
^{1}H-NMR(300MHz)δTMS $CDCl_3$:	0.02(9H, s, $-SiMe_3$),
	0.80 - 0.98(11H, m, -Me, $-CH_2TMS$),
	1.10 - 1.92(60H, m, $-CH_2-$),
	2.23 - 2.45(4H, m, $-COCH_2-$),
	3.15(1H, t, J = 9.8 Hz, H-1),
	3.31 - 3.38(1H, m, H-5),
	3.53 - 3.83(4H, m, H-4, H-6, OCH_2CH_2TMS),
	3.83 - 3.95(2H, m, H-1, H-6),
	4.07 - 4.20(2H, m, H-2, >CHOSEM),
	4.64 - 4.73(2H, m, $-OCH_2O-$),
	4.73 - 4.97(2H, m, H-3, >CHOCO-),
	6.16 - 6.20(1H, m, NH)

(the fourth step)
1,5-Anhydro-2-deoxy-3-O-{(2RS)-2-dodecanoyloxyhexadecanoyl)-4,6-O-phenoxyphosphoryl-2-[(3R)-3-{2-(trimethylsilyl)ethoxymethoxy)dodecanamido]-D-glucitol; (Compound 5b)

Compound 5b was obtained (820mg, yield: 71.4%) according to the same manner as that for the compound 5a, except that the compound 4b (1.0g) was used.

IR:	the same as that for the compound 5a
^{1}H-NMR(300MHz)δTMS $CDCl_3$:	0.02(9H, s, $-SiMe_3$),
	0.84 - 0.98(11H, m, -Me, $-CH_2TMS$),
	1.17 - 1.77(60H, m, $-CH_2-$),
	2.23 - 2.50(4H, m, $-COCH_2-$),
	3.20 - 3.32(1H, m, H-1),
	3.52 - 3.78(3H, m, H-5, $-OCH_2CH_2TMS$),
	3.87 - 3.98(1H, m, >CHOSEM),
	4.08 - 4.60(5H, m, H-1, H-2, H-4, H_2-6),
	4.61 - 4.72(2H, m, $-OCH_2O-$),
	4.72 - 4.99(1H, m, >CHOCO),
	5.09 - 5.23(1H, m, H-3),
	6.08 - 6.41(1H, m, NH),
	7.15 - 7.40(5H, m, Ph)

(the fifth step)
1,5-Anhydro-2-deoxy-3-O-{(2RS)-2-dodecanoyloxyhexadecanoyl}-2-{(3R)-3-hydroxydodecanamido)-4,6-O-phenoxyphosphoryl-D-glucitol; (Compound 6b)

The compound 6b was obtained (690mg, yield: 94.7%) according to the same manner for the compound 6a, except that the compound 5b (830mg) was used.

IR:	the same as that for the compound 5a
^{1}H-NMR(300MHz)δTMS $CDCl_3$:	0.89(9H, each t, J = 6.9 Hz, Me),
	1.23 - 1.96(60H, m, $-CH_2-$),
	2.20 - 2.46(4H, m, $-COCH_2-$),
	3.32 - 3.43(1H, m, H-1),
	3.57 - 4.57(7H, m, H-1, H-2, H-4, H-5, H_2-6, >CHOH),
	4.73 - 4.90(1H, m, >CHOCO),
	5.21 - 5.33(1H, m, H-3),
	6.29 - 6.64(1H, m, NH),
	7.14 - 7.42(5H, m, Ph)

(the sixth step)

Compound B was obtained (80mg, yield: 57.8%) according to the same manner for the compound A, except that the compound 6b (150mg) was used.

^{1}H-NMR:	Hydrogen signal on the benzene ring completely disappeared.
m. p.:	122-126 ° C (decomp.)
IR(film)cm^{-1}:	3586, 2928, 1738, 1649, 1261

Example 3

1,5-Anhydro-2-deoxy-3-O-{(2RS)-2-hexadecanoyloxydodecanoyl}-2-{(3RS)-3-hydroxyhexadecanamido)-4,6-O-hydroxyphosphoryl-D-glucitol; (Compound C)

(the first step)

1,5,-Anhydro-2-deoxy-4,6-O-isopropyriden-2-[(3RS)-3-{2-(trimethylsilyl)ethoxymethoxy} hexadecanamido]-D-glucitol; (Compound 2c)

Compound 2c was obtained (2.6g, yield: 81.7%) according to the same manner as that for the compound 2a, except that (RS)-3-{2-(trimethylsilyl)ethoxymethoxy}hexadecanoic acid (2.5g) was used.

IR(film)cm^{-1}:	3612, 1926, 1460, 1251, 1199, 1102
^{1}H-NMR(300MHz)δTMS CDCℓ$_3$:	0.03(9H, s, -SiMe$_3$),
	0.85 - 0.98(5H, m, -CH$_2$TMS, -Me),
	1.22 - 1.33(24H, m, -CH$_2$-),
	1.44, 1.52(6H, each s, >CMe$_2$),
	2.31 - 2.56(2H, m, -CH$_2$CO-),
	3.16 - 3.25(2H, m, H-1, H-5),
	3.54 - 3.65(4H, m, H-1, H-4, -OCH$_2$CH$_2$TMS),
	3.72(1H, t, J = 10.5 Hz, H-6),
	3.86 - 3.94(2H, m, H-6, >CHOSEM),
	3.98 - 4.13(2H, m, H-2, H-3),
	4.66 - 4.77(2H, m, -OCH$_2$O-),
	6.28 - 6.34(1H, m, NH)

(the second step)

1,5-Anhydro-2-deoxy-3-O-{(2RS)-2-hexadecanoyloxydodecanoyl}-4,6-O-isopropyriden-2-[(3RS)-3-{2-(trimethylsilyl)ethoxymethoxy}hexadecanamido]-D-glucitol; (Compound 3c)

Compound 3c was formed (2.8g, yield: 81.6%) according to the same manner as that for the compound 3a, except that the compound 2c (2.0g) and (RS)-2-hexadecanoyloxydodecanoic acid (1.5g) were used.

IR:	the same as that for the compound 3a
^{1}H-NMR(300MHz)δTMS CDCℓ$_3$:	0.03(9H, s, -SiMe$_3$),
	0.87 - 0.93(11H, m, -Me, -CH$_2$TMS),
	1.15 - 1.35(68H, -CH$_2$-),
	1.35, 1.36, 1.45, 1,47(6H, each s, >CMe$_2$),
	2.28 - 2.61(4H, m, -COCH$_2$O-),
	3.15 - 3.30(2H, m, H-1, H-5),
	3.48 - 3.95(6H, m, H-1, H-4, H$_2$-6, -OCH$_2$CH$_2$TMS),
	4.07 - 4.29(2H, m, H-2, >CHOSEM),
	4.63 - 4.80(2H, m, -OCH$_2$O-),
	4.86 - 5.02(2H, m, >CHOCO, H-3),
	6.00 - 6.57(1H, m, NH)

(the third step)

1,5-Anhydro-2-deoxy-3-O-{(2RS)-2-hexadecanoyloxydodecanoyl}-2-[(3RS)-3-{2-(trimethylsilyl)-ethoxymethoxy)hexadecanamido]-D-glucitol; (Compound 4c)

Compound 4c was obtained (1.7g, yield: 70.2%) according to the same manner as that for the compound 4a, except that the compound 3c (2.5g) was used.

IR:	the same as that for the compound 4a

^{1}H-NMR(300MHz)δTMS $CDCℓ_3$: 0.02(9H, s, $-SiMe_3$),
0.85 - 0.98(11H, m, -Me, $-CH_2TMS$),
1.19 - 1.90(68H, m, $-CH_2-$),
2.22 - 2.47(4H, m, $-COCH_2-$),
3.10 - 3.26(1H, m, H-1),
3.26 - 3.39(1H, m, H-5),
3.50 - 3.94(6H, m, H-1, H-4, H_2-6, $-OCH_2CH_2TMS$),
4.08 - 4.20(2H, m, H-2, >CHOSEM),
4.64 - 4.97(4H, m, H-3, $-OCH_2O-$, >CHOCO-),
6.15 - 6.48(1H, m, NH)

(the fourth step)
1,5-Anhydro-2-deoxy-3-O-{(2RS)-2-hexadecanoyloxydodecanoyl}-4,6-O-phenoxyphosphoryl-2-[(3RS)-3-{2-(trimethylsilyl)ethoxymethoxy}hexadecanamido-D-glucitol; (Compound 5c)

Compound 5c was obtained (1.3g, yield: 68.0%) according to the same manner as that for the compound 5a, except that the compound 4c (1.7g) was used.

IR: the same as that for the compound 5a
^{1}H-NMR(300MHz)δTMS $CDCℓ_3$: 0.03(9H, s, $-SiMe_3$),
0.87 - 0.99(11H, m, -Me, $-CH_2TMS$),
1.19 - 1.88(68H, m, $-CH_2-$),
2.27 - 2.68(4H, m, $-COCH_2-$),
3.20 - 3.37(1H, m, H-1),
3.51 - 3.82(3H, m, H-5, $-OCH_2CH_2TMS$),
3.82 - 3.99(1H, m, >CHOSEM),
4.11 - 4.60(5H, m, H-1, H-2, H-4, H_2-6),
4.60 - 5.00(3H, m, $-OCH_2O-$, >CHOCO-),
5.09 - 5.25(1H, m, H-3),
6.05 - 6.65(1H, m, NH),
7.16 - 7.41(5H, m, Ph)

(the fifth step)
1,5-Anhydro-2-deoxy-3-O-{(2RS)-2-hexadecanoyloxydodecanoyl}-2-{(3RS)-3-hydroxyhexadecanamido}-4,6-O-phenoxyphosphoryl-D-glucitol; (Compound 6c)

Compound 6c was obtained (1.2g, yield: 99.1%) according to the same manner as that for the compound 6a, except that the compound 5c (1.4g) was used.

IR: the same as that for the compound 6a
^{1}H-NMR(300MHz)δTMS $CDCℓ_3$: 0.88(9H, each t, J = 6.3 Hz, $-Me_3$),
1.19 - 1.92(68H, m, $-CH_2-$),
2.20 - 2.46(4H, m, $-COCH_2-$),
3.22 - 3.41(1H, m, H-1),
3.53 - 4.56(7H, m, H-1, H-2, H-4, H-5, H_2-6, >CHOH), 4.74 - 4.90(1H, m, >CHOCO),
5.18 - 5.31(1H, m, H-3),
6.22 - 6.83(1H, m, NH),
7.12 - 7.41(5H, m, Ph)

(the sixth step)

Compound C was obtained (140mg, yield: 72.6%) according to the same manner as that for the compound A, except that the compound 6c (210mg) was used.

^{1}H-NMR: Hydrogen signals on the benzene ring completely disappeared.
m. p.: 124-127° C (decomp.)
IR(film)cm^{-1}: 3586, 2926, 2856, 1738, 1638, 1257

Example 4
1,5-Anhydro-2-deoxy-3-O-{(2RS)-2-dodecylhexadecanoyl}-4,6-O-hydroxyphosphoryl-2-{(3R)-3-hydroxytetradecanamido}-D-glucitol; (Compound D)

(the second step)
1,5-Anhydro-2-deoxy-3-O-{(2RS)-2-dodecylhexadecanoyl}-4,6-O-isopropyriden-2-[(3R)-3-{2-(trimethylsilyl)-ethoxymethoxy}tetradecanamido]-D-glucitol; (Compound 3d)

An amorphous compound 3d was prepared (2.5g, yield: 90%) according to the same manner as that for the compound 3a, except that the compound 2a (1.6g) obtained in the first step of the example 1 and (RS)-2-dodecylhexadecanoic acid (1.9g) were used.

IR(film)cm^{-1}: 3480, 2900, 1720, 1655, 1530, 1460, 1370
^{1}H-NMR(300MHz)δTMS $CDCl_3$: 0.03(9H, s, Me_3Si),
0.83 - 0.94(11H, m, $-CH_2TMS$, -Me),
1.12 - 1.75(68H, m, $-CH_2-$),
1.32 - 1.43(6H, each s, CMe_2),
2.15 - 2.40(3H, m, $-COCH_2-$, -COCH<),
3.02 - 3.98(8H, m, H_2-1, H-4, H-5, H_2-6, $-OCH_2CH_2TMS$),
4.15 - 4.22(2H, m, H-2, >CH-OSEM),
4.65(2H, s, $-O-CH_2-O-$),
4.92(1H, t, J = 9.6 Hz, H-3),
6.18(1H, d, J = 7.1 Hz, NH)

(the third step)
1,5-Anhydro-2-deoxy-3-O-{(2RS)-2-dodecylhexadecanoyl}-2-[(3R)-3-{2-(trimethylsilyl)ethoxymethoxy}-tetradecanamido]-D-glucitol; (Compound 4d)

An amorphous compound 4d was formed (1.2g, yield: 64.8%) according to the same manner as that for the compound 4a, except that the compound 3d (1.9g) was used.

IR(nujol)cm^{-1}: 3500 - 3300, 1740, 1640, 1545
^{1}H-NMR(300MHz)δTMS $CDCl_3$: 0.02(9H, s, Me_3Si),
0.80 - 1.00(11H, m, $-CH_2TMS$, -Me),
1.10 - 1.71(68H, m, $-CH_2-$),
2.12 - 2.50(3H, m, $-COCH_2-$, -COCH<),
3.13(1H, t, J = 10.3 Hz, H-1),
3.26 - 3.37(1H, m, H-5),
3.51 - 3.99(6H, m, H-1, H-4, H_2-6, $-CH_2CH_2TMS$),
4.01 - 4.20(2H, m, >CH-OSEM, H-2),
4.67(2H, s, $-O-CH_2-O-$),
4.84(1H, t, J = 10.2 Hz, H-3),
6.22(1H, d, J = 7.3 Hz, NH)

(the fourth step)
1,5-Anhydro-2-deoxy-3-O-{(2RS)-2-dodecylhexadecanoyl}-4,6-O-phenoxyphosphoryl-2-[(3R)-3-{2-(trimethylsilyl)ethoxymethoxy} tetradecanamido]-D-glucitol; (Compound 5d)

An amorphous compound 5d was obtained (893 mg, yield: 74.8%) according to the same manner as that for the compound 5, except that the compound 4d (1.1g) was used.

IR(film)cm^{-1}: 3318, 2924, 2856, 1742, 1657, 1595, 1468, 1379, 1205, 963, 690
^{1}H-NMR(300MHz)δTMS $CDCl_3$: 0.06(9H, s, $-Me_3Si$),
0.71 - 1.04(11H, $-CH_2TMS$, -Me),
1.14 - 1.66(68H, m, $-CH_2-$),
2.20 - 2.50(3H, m, $-COCH_2-$, -COCH<),
3.11 - 3.30(1H, m, H-1),
3.54 - 3.80(3H, m, H-5, $-CH_2CH_2TMS$),
3.89 - 4.00(1H, m, >CH-OSEM),
4.11 - 4.58(5H, m, H-1, H-2, H-4, H_2-6),
4.70(2H, s, $-O-CH_2-O-$),

5.10, 5.16(1H, each t, J = 9.6 Hz, J = 9.6 Hz, H-3),
6.26, 6.33(1H, each d, J = 7.1 Hz, J = 7.2 Hz, NH),
7.13 - 7.46(5H, m, Ph)

(the fifth step)
1,5-Anhydro-2-deoxy-3-O-{(2RS)-2-dodecylhexadecanoyl}-2-{(3R)-3-hydroxytetradecanamido}-4,6-O-phenoxyphosphoryl-D-glucitol; (Compound 6d)

An amorphous compound 6d was obtained (758mg, yield: 96.7%) according to the same manner as that for the compound 6a, except that the compound 5d (758mg) was used.

IR(nujol)cm^{-1}: 3586 - 3366, 1736, 1640, 1539, 1164, 1048
^{1}H-NMR(300MHz)δTMS $CDCl_3$: 0.88(9H, t, J = 6.2 Hz, -Me),
1.09 - 1.56(68H, m, $-CH_2-$),
2.10 - 2.50(3H, m, $-COCH_2-$, -COCH<),
3.06 - 3.29(2H, m, H-1, OH),
3.51 - 3.62, 3,67 - 3.79(1H, each m, H-5),
3.87 - 3.99(1H, m, >CH-OH),
4.07 - 4.56(5H, m, H-1, H-2, H-4, H_2-6),
5.06, 5.13(1H, each t, J = 10.5 Hz, J = 9.9 Hz, H-3),
6.20, 6.28(1H, each d, J = 6.9 Hz, J = 5.7 Hz, NH),
7.10 - 7.44(5H, m, Ph)

(the sixth step)

A white powder compound D was obtained (38mg, yield: 83%) according to the same manner as that for the compound A with the exception that the compound 6d (50mg) was used.

^{1}H-NMR: Hydrogen signals on the benzene ring completely disappeared.
m. p.: 151.0-152.0 °C (decomp.)
IR(film)cm^{-1}: 2924, 2856, 1736, 1649, 1543, 1247

Example 5
1,5-Anhydro-2-deoxy-3-O-{(2RS)-2-dodecyloctadecanoyl}-2-{(3R)-3-hydroxydodecanamido}-4,6-O-hydroxyphosphoryl-D-glucitol; Compound E)

(the second step)
1,5-Anhydro-2-deoxy-3-O-{(2RS)-2-dodecyloctadecanoyl}-4,6-O-isopropyriden-2-[(3R)-3-{2-(trimethylsilyl)-ethoxymethoxy}dodecanamido]-D-glucitol; (Compound 3e)

A compound 3e was prepared (1.2g, yield: 67.1%) according to the same manner as that for the compound 3a, except that the compound 2b (1.0g) obtained in the first step of the example 2 and (RS)-2-dodecyloctadecanoic acid (853mg) were used.

IR: the same as that for the compound 3d
^{1}H-NMR: the same as that for the compound 3d

(the third step)
1,5-Anhydro-2-deoxy-3-O-{(2RS)-2-dodecyloctadecanoyl}-2-[(3R)-3-{2-(trimethylsilyl)-ethoxymethoxy}dodecanamido]-D-glucitol; (Compound 4e)

A compound 4e was obtained (838mg, yield: 71.7%) according to the same manner as that for the compound 4a with the exception that the compound 3e (1.2g) was used.

IR: the same as that for the compound 4d
^{1}H-NMR: the same as that for the compound 4d

(the fourth step)
1,5-Anhydro-2-deoxy-3-O-{(2RS)-2-dodecyloctadecanoyl}-4,6-O-phenoxyphosphoryl-2-[(3R)-3-{2-(trimethylsilyl)ethoxymethoxy}dodecanamido]-D-glucitol; (Compound 5e)

A compound 5e was obtained (177mg, yield: 78.2%) according to the same manner as that for the compound 5a with the exception that the compound 4e (200mg) was used.

IR: the same as that for the compound 5d

^{1}H-NMR: the same as that for the compound 5d

(the fifth step)

1,5-Anhydro-2-deoxy-3-O-{(2RS)-2-dodecyloctadecanoyl}-2-{(3R)-3-hydroxydodecanamido}-4,6-O-phenoxyphosphoryl-D-glucitol; (Compound 6e)

Compound 6e was obtained (133mg, yield: 85.8%) according to the same manner as that for the compound 6a, except that the compound 5e (177mg) was used.

IR: the same as that for the compound 6d

^{1}H-NMR: the same as that for the compound 6d

(the sixth step)

Compound E was formed (36mg, yield: 78.5%) according to the same manner as that for the compound A, except that the compound 6e (50mg) was used.

^{1}H-NMR: Hydrogen signal on the benzene ring completely disappeared.

m. p.: 154.5-155.5 °C (decomp.)

IR: the same as that for the compound D

Example 6

1,5-Anhydro-3-O-{(2RS)-2-decyloctadecanoyl}-2-deoxy-2-{(3RS)-3-hydroxyhexadecanamido}-4,6-O-hydroxyphosphoryl-D-glucitol; (Compound F)

(the second step)

1,5-Anhydro-3-O-{(2RS)-2-decyloctadecanoyl}-2-deoxy-4,6-O-isopropyriden-2-[(3RS)-3-{2-(trimethylsilyl)-ethoxymethoxy}hexadecanamido]-D-glucitol; (Compound 3f)

A compound 3f was prepared (822mg, yield: 48.6%) according to the same manner as that for the compound 3a, except that the compound 2c (1.0g) obtained in the first step of the example 3 and (RS)-2-decyloctadecanoic acid (724mg) were used.

IR: the same as that for the compound 3d

^{1}H-NMR: the same as that for the compound 3d, except for the -CH_2- integration value.

(the third step)

1,5-Anhydro-3-O-{(2RS)-2-decyloctadecanoyl)-2-deoxy-4,6-O-phenoxyphosphoryl-2-[(3RS)-3-{2-(trimethylsilyl)ethoxymethoxy} hexadecanamido]-D-glucitol; (Compound 4f)

Compound 4f was obtained (565mg, yield: 76.6%) according to the same manner as that for the compound 4a with the exception that the compound 3f (822mg) was used.

IR: the same as that for the compound 4d

^{1}H-NMR: the same as that for the compound 4d except for the -CH_2- integration value.

(the fourth step)

1,5-Anhydro-3-O-{(2RS)-2-decyloctadecanoyl}-2-deoxy-2-[(3RS)-3-{2-(trimethylsilyl)-ethoxymethoxy}hexadecanamido]-D-glucitol; (Compound 5f)

Compound 5f was obtained (184mg, yield: 81.6%) according to the same manner as that for the compound 5a with the exception that the compound 4f (200mg) was used.

IR: the same as that for the compound 5d

^{1}H-NMR: the same as that for the compound 5d except for the -CH_2- integration value.

(the fifth step)

1,5-Anhydro-3-O-{(2RS)-2-decyloctadecanoyl}-2-deoxy-2-{(3RS)-3-hydroxyhexadecanamido}-4,6-O-phenoxyphosphoryl-D-glucitol; (Compound 6f)

A compound 6f was obtained (145mg, yield: 89.7%) according to the same manner as that for the compound 6a, except for the compound 5f (184mg) was used.

IR: the same as that for the compound 6d

^{1}H-NMR: the same as that for the compound 6d except for the -CH_2- integration value.

(the sixth step)

A compound F was obtained (31mg, yield: 60.0%) according to the same manner as that for the compound A, except that the compound 6f (50mg) was used.

^{1}H-NMR: Hydrogen signals on the benzene ring completely disappeared.

m. p.: 159.7-161.4°C (decomp.)

IR: the same as that for the compound D

Example 7

1,5-Anhydro-2-deoxy-4,6-O-hydroxyphosphoryl-2-{(3R)-3-hydroxytetradecanamido}-3-O-{(3R)-3-tetradecanoyloxytetradecanoyl}-D-glucitol; (Compound G)

(the second step)

1,5-Anhydro-2-deoxy-4,6-O-isopropyriden-3-O-{(3R)-3-tetradecanoyloxytetradecanoyl}-2-[(3R)-3-{2-(trimethylsilyl)ethoxymethoxy}tetradecanamido]-D-glucitol; (Compound 3g)

An amorphous compound 3g was prepared (2.0g, yield: 79.6%) according to the same manner as that for the compound 3a with the exception that the compound 2a (1.38g) obtained in the first step of the example 1 and (R)-3-tetradecanoyloxytetradecanoic acid (1.12g) were used.

[α]D: +0.05° (c = 1.25, $CHC\ell_3$)

IR(film)cm^{-1}: 3316, 2926, 2858, 1738, 1647, 1543, 851, 835

^{1}H-NMR(300MHz)δTMS $CDC\ell_3$: 0.02(9H, s, $SiMe_3$),
0.78 - 0.98(11H, m, -Me, -CH_2TMS),
1.08 - 1.66(62H, m, -CH_2-),
1.33, 1.46(6H, each s, >CMe_2),
2.17 - 2.39(4H, m, -$COCH_2$-),
2.47 - 2.65(2H, AB part of ABX, J_{AB} = 32.2 Hz, J_{AX} = 7.2 Hz, J_{BX} = 9.5 Hz, -$NHCOCH_2$-),
3.10(1H, t, J = 9.9 Hz, H-1),
3.16 - 3.28(1H, m, H-5),
3.49 - 3.94(6H, m, H-1, H-4, H_2-6, CH_2CH_2TMS),
4.02 - 4.20(2H, m, H-2, >CHOSEM),
4.62 - 4.68(2H, AB, J_{AB} = 13.1 Hz, -OCH_2O-),
4.89(1H, t, J = 10.4 Hz, H-3),
5.09 - 5.20(1H, m, -$COCH_2CHCO$),
6.22(1H, d, J = 6.3 Hz, NH)

(the third step)

1,5-Anhydro-2-deoxy-3-O-{(3R)-3-tetradecanoyloxytetradecanoyl)-2-[(3R)-3-{2-(trimethylsilyl)-ethoxymethoxy)tetradecanamido]-D-glucitol; (Compound 4g)

An amorphous compound 4g was obtained (1.6g, yield: 84.2%) according to the same manner as that for the compound 4a with the exception that the compound 3g (2.0g) was used.

[α]D: +5.55° (c = 1.25, $CHC\ell_3$)

IR(film)cm^{-1}: 3580 - 3190, 2922, 2856, 1736, 1651, 1551, 861, 835

^{1}H-NMR(300MHz)δTMS $CDC\ell_3$: 0.02(9H, s, $SiMe_3$),
0.80 - 1.00(11H, m, -Me, -CH_2TMS),
1.12 - 1.71(62H, m, -CH_2-),
2.24 - 2.41(4H, m, -$COCH_2$-),
2.53(2H, d, J = 5.4 Hz, -NH, -$COCH_2$-),
3.11(1H, t, J = 10.8 Hz, H-1),
3.26 - 3.38(1H, m, H-5),
3.43 - 4.21(8H, m, H-1, H-2, H-4, H_2-6, -CH_2CH_2TMS, >CHOSEM),

4.70 - 4.63(2H, AB, J_{AB} = 14.5 Hz, -OCH_2O-),
4.81(1H, t, J = 10.3 Hz, H-3),
5.05 - 5.17(1H, m, >CHCO-),
6.40(1H, d, J = 7.0 Hz, NH)

(the fourth step)
1,5-Anhydro-2-deoxy-4,6-O-phenoxyphosphoryl-3-O-{(3R)-3-tetradecanoyloxytetradecanoyl}-2-[(3R)-3-{2-(trimethylsilyl)ethoxymethoxy}tetradecanamido]-D-glucitol; (Compound 5g)

An amorphous compound 5g was obtained according to the same manner as that for the compound 5a with the exception that the compound 4g (1.02g) was used.

IR(film)cm^{-1}: 3586, 2926, 1744, 1667, 1539, 1466, 1379
^{1}H-NMR(300MHz)δTMS $CDCl_3$: 0.11, 0.02(9H, each s, -$SiMe_3$),
0.81 - 1.00(11, m, -Me, -CH_2TMS),
1.12 - 1.67(62H, m, -CH_2-),
2.20 - 2.66(6H, m, -$COCH_2$-),
3.08 - 3.28(1H, m, H-3),
3.50 - 3.79(3H, m, H-5, -CH_2CH_2TMS),
3.81 - 3.97(1H, m, >CHOSEM),
4.05 - 4.55(5H, m, H-1, H-2, H-4, H_2-6),
4.61 - 4.79(2H, m, -OCH_2O-),
5.01 - 5.28(2H, m, H-3, >CHOCO),
6.40 - 6.51(1H, m, NH),
7.24 - 7.45(5H, m, Ph)

(the fifth step)
1,5-Anhydro-2-deoxy-2-{(3R)-3-hydroxytetradecanamido}-4,6-O-phenoxyphosphoryl-3-O-{(3R)-3-tetradecanoyloxytetradecanoyl}-D-glucitol; (Compound 6g)

An amorphous compound 6g (320mg, yield: 44.2%) was obtained according to the same manner as that for the compound 6a with the exception that the compount 5g (821mg) was used.

IR(film)cm^{-1}: 3586, 1742, 1651, 1543, 1168, 1052
^{1}H-NMR(300MHz)δTMS $CDCl_3$: 0.88(9K, t, J = 5.0 Hz, Me),
1.18 - 1.70(62H, m, -CH_2-),
2.20 - 2.63(6H, m, -$COCH_2$-),
3.18 - 3.42(2H, m, H-1, OH),
3.51 - 3.62, 3.70 - 3.80(1H, each m, H-5),
3.83 - 3.96(1H, m, >CHOH),
4.02 - 4.57(5H, m, H-1, H-2, H-4, H_2-6),
5.04 - 5.21(2H, m, H-3, >CHOCO),
6.67, 6.77(1H, each d, J = 6.8 Hz, J = 4.9 Hz, NH),
7.14 - 7.43(5H, m, Ph)

(the sixth step)

A white powder of compound G was obtained (90mg, yield: 97.7%) according to the same manner as that for the compound A, except that the compound 6g (100mg) was used.

^{1}H-NMR: Hydrogen signals on the benzene ring completely disappeared.
[α]D: -1.55° (c = 1.1, $CHCl_3$: MeOH = 1.1)
m. p.: 274.1-277.9°C (decomp.)
IR(film)cm^{-1}: 2858, 1719, 1651, 1462

Example 8
1,5-Anhydro-2-deoxy-4,6-O-hydroxyphosphoryl-2-{(3R)-3-hydroxytetradecanamido}-3-O-{(3RS)-3-undecylheptadecanoyl}-D-glucitol; (Compound H)

(the second step)
1,5-Anhydro-2-deoxy-4,6-O-isopropyriden-2[(3R)-3-{2-(trimethylsilyl)ethoxymethoxy}tetradecanamido]-3-O-{(3RS)-3-undecylheptadecanoyl}-D-glucitol; (Compound 3h)

An amorphous compound 3h was prepared (4.12g, yield: 91%) according to the same manner as that for the compound 3h, except that the compound 2a (3.0g) obtained in the first step of the example 1 and (RS)-3-undecylheptadecanoic acid (2.0g) were used.

IR(film)cm^{-1}: 3320, 2900, 1735, 1645, 1545, 1470, 1383
^{1}H-NMR(300MHz)δTMS $CDCl_3$: 0.03(9H, s, Me_3Si),
0.86 - 0.97(11H, m, $-CH_2TMS$, -Me),
1.18 - 1.60(66H, m, $-CH_2-$),
1.36, 1.47(6H, each s, CMe_2),
1.85(1H, m, -CH<),
2.20 - 2.40(4H, m, $-CH_2CO-$),
3.10 - 4.00(8H, m, H_2-1, H-4, H-5, H_2-6, $-O-CH_2CH_2TMS$),
4.16(2H, m, H-2, -CH-OSEM),
4.66, 4.68(2H, AB, J_{AB} = 6.9 Hz, $-OCH_2O-$),
4.94(1H, t, J = 9.6 Hz, H-3),
6.27(1H, d, J = 7.0 Hz, NH)

(the third step)
1,5-Anhydro-2-deoxy-2-[(3R)-3-{2-(trimethylsilyl)ethoxymethoxy)tetradecanmido]-3-O-{(3RS)-3-undecylheptadecanoyl}-D-glucitol; (Compound 4h)

An amorphous compound 4h was formed (1.84g, yield: 91%) according to the same manner as that for the compound 4a with the exception that the compound 3h (2.79g) was used.

IR(film)cm^{-1}: 3600 - 3100, 2900, 1720, 1650, 1540, 1463, 1380
^{1}H-NMR(300MHz)δTMS $CDCl_3$: 0.02(9H, s, $-SiMe_3$),
0.85 - 0.96(11H, m, $-CH_2TMS$, -Me),
1.10 - 1.65(66H, m, $-CH_2-$),
1.85(1H, m, -CH<),
2.20 - 2.40(4H, m, $-COCH_2-$),
2.65(1H, brs, -OH),
3.13(1H, t, J = 10.0 Hz, H-1),
3.32(1H, m, H-5),
3.52 - 3.95(6H, m, H-1, $-CH_2-CH_2TMS$, H-4, H_2-6),
4.0 - 4.17(2H, m, H-2, -CH-OSEM),
4.63, 4.69(2H, AB, J = 7.0 Hz, $-OCH_2O-$),
4.85(1H, t, J = 9.4 Hz, H-3),
6.29(1H, d, J = 7.3 Hz, NH)

(the forth step)
1,5-Anhydro-2-deoxy-4,6-O-phenoxyphosphoryl-2-[(3R)-3-{2-(trimethylsilyl)-ethoxymethoxy}tetradecanamido]-3-O-{(3RS)-3-undecylheptadecanoyl}-D-glucitol; (Compound 5h)

An amorphous compound 5h was obtained (1.0g, yield: 80.5%) according to the same manner as that for the compound 5a with the exception that the compound 4h (1.1g) was used.

IR(film)cm^{-1}: 3308, 2926, 1744, 1659, 1595, 1466, 1707, 1379, 944, 665
^{1}H-NMR(300MHz)δTMS $CDCl_3$: 0.02(9H, s, $-SiMe_3$),
0.80 - 0.99(11H, m, -Me, $-CH_2TMS$),
1.11 - 1.60(66H, m, $-CH_2-$),
1.69 - 1.90(1H, m, >CH-),
2.14 - 2.41(4H, m, $-COCH_2-$),
3.08 - 3.27(1H, m, H-1),
3.50 - 3.77(3H, m, H-5, $-CH_2CH_2TMS$),
3.81 - 3.92(1H, m, >CHOSEM),
4.04 - 4.54(5H, m, H-1, H-2, H-4, H_2-6),
4.61 - 4.72(2H, m, $-OCH_2O-$),

5.02 - 5.18(1H, m, H-3),
6.29, 6.36(1H, each d, J = 7.5 Hz, J = 4.9 Hz, NH),
7.10 - 7.40(5H, m, Ph)

(the fifth step)
1,5-Anhydro-2-deoxy-2-{(3R)-3-hydroxytetradecanamido]-4,6-O-phenoxyphosphoryl-3-O-{(3RS)-3-undecylheptadecanoyl}-D-glucitol; (Compound 6h)

A compound 6h was obtained (751mg, yield: 86.0%) according to the same manner as that for the compound 6a with the exception that the compound 5h (1.0g) was used.

IR(film)cm^{-1}: 3586, 3296, 1742, 1651, 1543, 1168, 1052
^{1}H-NMR(300MHz)δTMS $CDCl_3$: 0.88(9H, t, J = 6.4 Hz, -Me),
1.14 - 1.52(66H, m, $-CH_2-$),
1.70 - 1.90(1H, m, >CH-),
2.14 - 2.45(4H, m, $-COCH_2$),
3.13 - 3.31(1H, m, H-1),
3.52 - 3.64, 3.69 - 3.79(1H, each m, H-5),
3.85 - 3.99(1H, m, >CHOH),
4.08 - 4.57(5H, m, H-1, H-2, H-4, H_2-6),
5.10 - 5.29(1H, m, H-3),
6.27, 6.39(1H, each d, J = 7.1 Hz, J = 7.3 Hz, NH),
7.11 - 7.42(5H, m, Ph)

(the sixth step)

A white power H was formed (38mg, yield: 82.7%) according to the same manner as that for the compound A with the exception that the compound 6h (100mg) was used.

^{1}H-NMR: Hydrogen signals on the benzene ring completely disappeared.
m. p.: 153.2-156.3 °C (decomp.)
IR(film)cm^{-1}: 2922, 1649, 1543, 1460

Example 9
1,5-Anhydro-2-deoxy-3-O-(2-dodecyltetradecanoyl)-4,6-O-hydroxyphosphoryl-2-tetradecanamido-D-glucitol; (Compound I)

(the first step)
1,5-Anhydro-2-deoxy-4,6-O-isopropyriden-2-tetradecanamido-D-glucitol; (Compound 2i)

A compound 2i was formed according to the same manner as that for the compound 2a with the exception that tetradecanoic acid (2.3g) was used.

[α]D: -9.4° (c = 1.01, $CHCl_3$)
m. p.: 108.0 - 109.0 °C
IR(film)cm^{-1}: 3308, 2922, 2854, 1647, 1547, 1468
^{1}H-NMR(300MHz)δTMS $CDCl_3$: 0.88(9H, t, J = 6.7 Hz, Me),
1.16 - 1.38(20H, m, $-CH_2-$),
1.43, 1.52(6H, each s, $>CMe_2$),
1.57 - 1.69(2H, m, $-COCH_2CH_2-$),
2.14 - 2.28(2H, m, $-COCH_2-$),
3.18(1H, t, J = 10.8 Hz, H-1),
3.11 - 3.22(1H, m, H-5),
3.47 - 3.63(2H, m, H-1, H-4),
3.72(1H, t, J = 10.6 Hz, H-6),
3.90(1H, dd, J = 5.4 Hz, J = 10.8 Hz, H-6),
3.94 - 4.08(1H, m, H-2),
4.15(1H, dd, J = 5.4 Hz, J = 10.9 Hz, H-3),
5.54(1H, d, J = 6.6 Hz, NH)

(the second step)
1,5-Anhydro-2-deoxy-3-O-(2-dodecyltetradecanoyl)-4,6-O-isopropyriden-2-tetradecanamido-D-glucitol; (Compound 3i)

A compound 3i was obtained (1.3g, yield: 84.0%) according to the same manner as that for the compound 3a with the exception that the compound 2i (833mg) and 2-tetradecyldecanoic acid (776mg) were used.

[α]D:	-8.5° (c = 1.27, $CHC\ell_3$)
m. p.:	52.8 - 54.0° C
IR(film)cm^{-1}:	3298, 2922, 2854, 1734, 1649, 1545, 1468
^{1}H-NMR(300MHz)δTMS $CDC\ell_3$:	0.88(9H, t, J = 6.7 Hz, Me), 1.10 - 1.65(66H, m, $-CH_2-$), 1.35, 1.47(6H, each s, $>CMe_2$), 2.09(2H, t, J = 7.7 Hz, $-COCH_2-$), 2.26 - 2.42(1H, m, COCH<), 3.12(1H, t, J = 10.0 Hz, H-1), 3.20 - 3.32(1H, m, H-5), 3.65 - 3.79(2H, m, H-1, H-6), 3.92 - (1H, dd, J = 5.2 Hz, J = 10.7 Hz, H-6), 4.06 - 4.27(2H, m, H-4, H-2), 4.92(1H, t, H = 9.7 Hz, H-3), 5.89(1H, d, J = 6.9 Hz, NH)

(the third step)
1,5-Anhydro-2-deoxy-3-O-(2-dodecyltetradecanoyl)-2-tetradecanamido-D-glucitol; (Compound 4i)

A compound 4i was obtained (1.1g, yield: 84.0%) according to the same manner as that for the compound 4a with the exception that the compound 3i (1.2g) was used.

[α]D:	-0.089° (c = 1.05, $CHC\ell_3$)
m. p.:	99.0° C
IR(film)cm^{-1}:	3372, 3320, 2922, 2856, 1736, 1647, 1537, 1466
^{1}H-NMR(300MHz)δTMS $CDC\ell_3$:	0.88(9H, t, J = 6.9 Hz, Me), 1.08 - 1.67(66H, m, $-CH_2-$), 2.09(2H, t, J = 7.8 Hz, $-COCH_2-$), 2.27 - 2.46(1H, m, -COCH<), 3.13(1H, t, J = 10.5 Hz, H-1), 3.23 - 3.34(1H, m, H-5), 3.68 - 3.96(3H, m, H-1, H_2-6), 3.98 - 4.19(2H, m, H-2, H-4), 4.89(1H, t, J = 9.7 Hz, H-3), 6.07(1H, d, J = 7.0 Hz, NH)

(the fourth step)
1,5-Anhydro-2-deoxy-3-O-(2-dodecyltetradecanoyl)-4,6-O-phenoxyphosphoryl-2-tetradecanamido-D-glucitol; (Compound 5i)

Compound 5i was obtained (969mg, yield: 84.0%) according to the same manner as that for the compound 5a with the exception that the compound 4i (969mg) was used.

m. p.:	86.4 - 87.0° C
IR(film)cm^{-1}:	3380, 2918, 2854, 1738, 1669, 1595, 1493, 1468, 1379, 1301, 1207, 768
^{1}H-NMR(300MHz)δTMS $CDC\ell_3$:	0.88(9H, t, J = 6.6 Hz, Me), 1.11 - 1.72(66H, m, $-CH_2-$), 2.90(2H, t, J = 7.6 Hz, $-COCH_2-$), 2.26 - 2.49(1H, m, -COCH<), 3.13, 3.19(1H, each t, J = 10.5 Hz, J = 10.2 Hz, H-1), 3.52 - 3.63, 3.67 - 3.79(1H, each m, H-5), 4.04 - 4.53(5H, m, H-1, H-2, H-4, H_2-6),

5.03, 5.11(1H, each t, J = 9.9 Hz, J = 9.8 Hz, H-3),
5.86, 5.96(1H, each d, J = 6.8 Hz, J = 7.0 Hz, NH),
7.10 - 7.41(5H, m, Ph)

(the sixth step)

Compound I was formed (219mg, yield: 41.0%) according to the same manner as that for the compound A, with the exception that the compound (5i) (585mg) was used.

[α]D: -0.39° (c = 1.00, $CHC\ell_3$)
m. p.: 93.0 - 96.0° C
IR(film)cm^{-1}: 3296, 2924, 2856, 1736, 1651, 1543, 1468, 1379, 1257, 1178

Example 10
1,5-Anhydro-2-deoxy-4,6-O-hydroxyphosphoryl-2-{(3R)-3-hydroxytetradecanamido}-3-O-{(3RS)-3-tetradecyloxytetradecanoyl}-D-glucitol; (Compound J)

(the second step)
1,5-Anhydro-2-deoxy-4,6-O-isopropyriden-3-O-{(3RS)-3-tetradecyloxytetradecanoyl}-2-[(3R-3-{2-(trimethylsilyl)ethoxymethoxy}tetradecanamido]-D-glucitol; (Compound 3j)

An amorphous compound 3j was prepared (8.1g, yield: 87.5%) according to the same manner as that for the compound 3a, with the exception that the compound 2a (5.3g) obtained in the first step of the example 1 and (RS)-3-tetradecyloxytetradecanoic acid (4.1g) were used.

IR(KBr)cm^{-1}: 3308, 2926, 2858, 1734, 1647, 1547, 1466, 1371, 1251, 1201, 1106, 1056
^{1}H-NMR(300MHz)δTMS $CDC\ell_3$: 0.02(9H, s, $SiMe_3$),
0.75 - 1.00(11H, m, Me, $-CH_2TMS$),
1.00 - 1.61(65H, m, $-CH_2-$, >CH-),
1.34, 1.46(each s, $Me_2C<$),
2.19 - 2.70(4H, m, $-COCH_2-$),
3.04 - 3.96(H_2-1, H-4, H-5, H_2-6, $-CH_2CH_2TMS$, $-OCH_2CH_2-$),
4.05 - 4.22(2H, m, H-2, >CHOSEM),
4.57 - 4.72(2H, m, $-OCH_2O-$),
4.86 - 5.00(1H, m, H-3),
6.26(1H, d, J = 6.9 Hz, NH)

(the third step)
1,5-Anhydro-2-deoxy-3-O-{(3RS)-3-tetradecyloxytetradecanoyl}-2-[(3R)-3-{2-(trimethylsilyl)-ethoxymethoxy}tetradecanamido]-D-glucitol; (Compound 4j)

An amorphous compound 4j was obtained (6.1g, yield: 78.5%) according to the same manner as that for the compound 4a, with the exception that the compound 3j (8.0g) was used.

IR(KBr)cm^{-1}: 3310, 2926, 2858, 1729, 1657, 1539, 1466, 1379, 1305, 1251, 1158, 1104
1H-NMR(300MHz)δTMS $CDC\ell_3$: 0.02(9H, m, $SiMe_3$),
0.78 - 1.00(11H, m, Me, $-CH_2TMS$),
1.00 - 1.70(65H, m, $-CH_2-$, >CH-),
2.21 - 2.78(4H, m, $-COCH_2-$),
3.12(1H, J = 10.5 Hz, H-1),
3.26 - 3.95(9H, m, H-1, H-4, H-5, H_2-6, $-CH_2CH_2TMS$, $-OCH_2CH_2-$),
4.00 - 4.21(2H, m, H-2, >CHOSEM),
4.65, 4.68(2H, AB, J_{AB} = 6.8 Hz, $-OCH_2O-$),
4.71 - 4.90(1H, m, H-3), 6.27 - 6.60(1H, m, NH)

(the fourth step)
1,5-Anhydro-2-deoxy-4,6-O-phenoxyphosphoryl-3-O-{(3RS)-3-tetradecyloxytetradecanoyl}-2-[(3R)-3-{2-(trimethylsilyl)ethoxymethoxy} tetradecanamido]-D-glucitol; (Compound 5j)

An amorphous compound 5j was formed (878g, yield: 77.6%) according to the same manner as that for the compound 5a, with the exception that the compound 4j (1.0g) was used.

IR(KBr)cm^{-1}: 2926, 2858, 1744, 1657, 1543, 1493, 1466, 1305, 1251, 1104, 1054

^{1}H-NMR(300MHz)δTMS $CDCl_3$: 0.02(9H, m, $SiMe_3$),
0.77 - 1.00(11H, m, Me, -CH_2TMS),
1.00 - 1.61(65H, m, -CH_2-, >CH-),
2.15 - 2.72(4H, m, -$COCH_2$-),
3.09 - 4.55(12H, m, H_2-1, H-2, H-4, H-5, H_2-6, -CH_2CH_2TMS, -OCH_2CH_2, >CHOSEM),
4.55 - 4.72(2H, m, -OCH_2O-),
5.01 - 5.20(1H, m, H-3),
6.22 - 6.40(1H, m, NH),
7.10 - 7.40(5H, m, Ph)

(the fifth step)

1,5-Anhydro-2-deoxy-2-{(3R)-3-hydroxytetradecanamido}-4,6-O-phenoxyphosphoryl-3-O-(3RS)-3-tetradecyloxytetradecanoyl}-D-glucitol; (Compound 6j)

An amorphous compound 6j was obtained (710g) according to the same manner as that for the compound 6a, with the exception that the compound 5j (845mg) was used.

IR(KBr)cm^{-1}: 3296, 2922, 2856, 1742, 1655, 1595, 1547, 1491, 1468, 1309, 1207, 1174

^{1}H-NMR(300MHz)δTMS $CDCl_3$: 0.88(9H, t, J = 6.4 Hz, Me),
1.00 - 1.63(65H, m, -CH_2-, >CH-),
2.10 - 2.71(4H, m, -$COCH_2$-),
3.18 - 4.60(10H, m, H_2-1, H-2, H-4, H-5, H_2-6, >CHOH, -OCH_2CH_2-),
5.11 - 5.31(3H, m, H-3),
6.40 - 6.70(1H, m, NH),
7.11 - 7.45(5H, m, Ph)

(the sixth step)

A white powder of compound (J) was obtained (91mg, yield: 93.4%) according to the same manner as that for the compound A, with the exception that the compound 6j (100mg) was used.

^{1}H-NMR: Hydrogen signals on the benzene ring completely disappeared.

m. p.: 161-164 °C

IR(KBr)cm^{-1}: 3272, 2924, 2854, 1740, 1647, 1543, 1468, 1363, 1259, 1176

Example 11

2-deoxy-4,6-O-hydroxyphosphoryl-2{(3R)-3-hydroxytetradecanamido}-3-O-{(2RS)-tetradecanoyloxytetradecanoyl}-D-glucopyranose; (Compound K)

(the seventh step)

30mg of 2-deoxy-2-{(3R)-3-hydroxytetradecanamido}-4-O-phosphono-3-O-{(2RS)-2-tetradecanoyloxytetradecanoyl}-D-glucopyranose(7k) which can be produced according to the known manner (Japanese Patent Disclosure No. 62888/90) was dissolved in a mixture solvent of tetrahydrofuran: chloroform (1:1) (10mℓ). To the resultant solution, DCC (5mg) was added, followed by stirring for three hours. The reacted solution was subjected to a Sephadex column (LH-20, chloroform:methanol = 1:1). Further, the solution was lyophilized by utilizing 1,4-dioxane to obtain a compound K.

m. p.: 158-160 °C

IR(KBr)cm^{-1}: 3300, 2950, 2860, 1740, 1680, 1590,

$C_{48}H_{89}NO_{12}P$ (903.21)			
theoretical value:	C = 63.83%,	H = 9.93%,	N = 1.55%
actual value:	C = 64.04%,	H = 9.76%,	N = 1.49%

Example 12
2-Deoxy-3-O-{(2RS)-2-dodecylhexadecanoyl}-4,6-O-hydroxyphosphoryl-2-{(3R)-3-hydroxytetradecanamido}-D-glucopyranose; (Compound L)

(the seventh step)

Compound L was obtained according to the same manner as that for the compound K, with the exception that 2-deoxy-3-O-{(2RS)-2-dodecylhexadecanoyl}-2-{(3R)-3-hydroxytetradecanamido}-4-O-phosphono-D-glucopyranose (71) which can be produced in the known method (Japanese Patent Disclosure No. 25494/90) was used.

m. p.: 167-169 °C

IR(KBr)cm^{-1}: 3400, 2930, 2850, 1720, 1640, 1550

$C_{48}H_{93}NO_{11}P$ (891.24)			
theoretical value:	C = 64.69%,	H = 10.52%,	N = 1.57%
actual value:	C = 64.65%,	H = 10.29%,	N = 1.82%

Example 13
2-Deoxy-4,6-O-hydroxyphosphoryl-2-{(3R)-3-hydroxytetradecanamido}-3-O-{(3R)-3-tetradecanoyloxytetradecanoyl}-D-glucopyranose; (Compound M)

(the seventh step)

Compound M was obtained according to the same manner as that for the compound K, with the exception that 2-deoxy-2-{(3R)-3-hydroxytetradecanamido}-4-O-phosphono-3-O-{(3R)-3-tetradecanoyloxytetradecanoyl}-D-glucopyranose (7m) which can be produced by the known method (Japanese Disclosure No. 62889/90) was used.

[α]D: -2.0 ° (c = 0.5, $CHCl_3$:MeOH = 1.1)

m. p.: 168-170 °C

$C_{48}H_{89}NO_{12}P$ (903.32)						
theoretical value:	C	63.83%,	H	9.93%,	N	1.55%
actual value:	C	63.83%,	H	10.02%,	N	1.33%

Example 14
2-Deoxy-4,6-O-hydroxyphosphoryl-2-{(3R)-3-hydroxytetradecanamido)-3-O-{(3RS)-3-undecylheptadecanoyl}-D-glucopyranose; (Compound N)

(the seventh step)

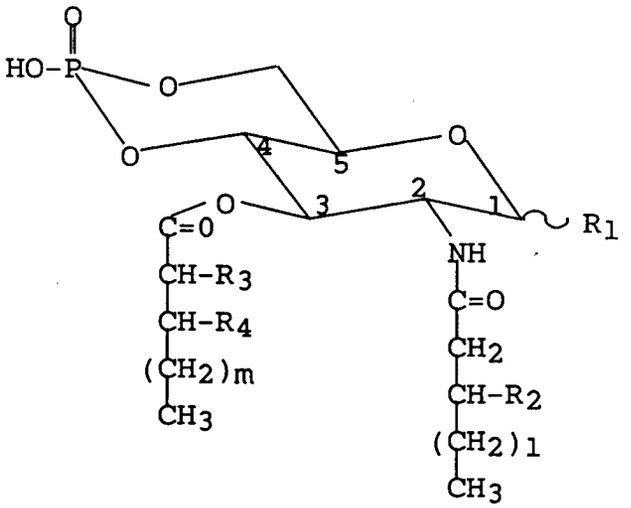
Compound N was obtained according to the same manner as that for the compound K, with the exception that 2-deoxy-2-{(3R)-3-hydroxytetradecanamido}-4-O-phosphono-3-O-{(3RS)-3-undecylheptadecanoyl)-D-glucopyranose (7n) which can be produced by the same known method (Japanese Patent No. 241866/89) was used.

m. p.: 176-179 °C

$C_{48}H_{91}NO_{10}P$ (873.23)			
theoretical value:	C = 66.02%,	H = 10.50%,	N = 1.60%
actual value:	C = 66.20%,	H = 10.24%,	N = 1.89%

Claims

1. 4,6-O-hydroxyphosphoryl-glucosamine derivatives as shown in the following formula [I] and its pharmaceutically-acceptable salt:



[I]

wherein R_1 and R_2 indicate a hydrogen atom or a hydroxy group; one of R_3 and R_4 indicates -OCO-$(CH_2)_nCH_3$, -$CH_2(CH_2)_nCH_3$ or -O-$CH_2(CH_2)_nCH_3$, and the other indicates a hydrogen atom; l is an integer of 4-16; m is an integer of 4-16; and n is an integer of 6-18.

INTERNATIONAL SEARCH REPORT

International Application No PCT/JP91/00475

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl[5] C07H13/04//A61K31/70

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC	C07H11/04, C07H13/00-06

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	JP, A, 02-62889 (Japan Tobacco Inc.), March 2, 1990 (02. 03. 90), (Family: none)	1
A	JP, A, 02-25494 (Japan Tobacco Inc.), January 26, 1990 (26. 01. 90), (Family: none)	1
A	JP, A, 01-213290 (Toho Yakuhin Kogyo K.K.), August 28, 1989 (28. 08. 89), (Family: none)	1

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
June 10, 1991 (10. 06. 91)	June 24, 1991 (24. 06. 91)
International Searching Authority	**Signature of Authorized Officer**
Japanese Patent Office	